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The Journal of Allergy

VOL. 11 JANUARY, 1940 NO. 2

Original Articles

ANTIGENIC STUDIES BY THE DALE TEST*

II. THE ANTIGENICITY OF HOUSE DUST

STANLEY F. HAMPTON, M.D., AND ARTHUR STULL, PH.D.
NEW YORK, N. Y.

THE purpose of this investigation[1] was to study the antigenicity of house dust extract with particular reference to two factors: (1) the part played by common household inhalants other than dust and (2) the "unknown factor" as an antigen, first pointed out by Cooke[2] when he introduced house dust as a causative allergen in bronchial asthma. The study was carried out by the Dale test. In order to prevent confusion in the text of this presentation, the term "inhalant" is used to denote air-borne allergens other than house dust.

Ramsdell and Walzer[3] were unable to sensitize guinea pigs to house dust extract. Coulson and Stevens,[4] however, recently reported the production of gross anaphylaxis in five guinea pigs sensitized by alum-precipitated house dust extract. Five of the seven normal control animals showed symptoms simulating anaphylaxis, which the authors called "anaphylactoid" and attributed to a "nonspecific toxic factor."

METHODS

Four extracts were prepared from dusts of different sources. A-dust was a sample collected from 40 different sources (apartments, houses, and offices). B-dust was a sample collected from a single patient's house, in which no animals were allowed because of the patient's sensitivity. C-dust was collected from a physician's office, in which no animals were admitted, but in which there were a few feather pillows. D-dust was a sample of dust from several different house sources (approximately one-fifth the number of A-dust).

The dusts were treated and extracted as follows: Equal quantities of B-, C-, and D-dusts were washed with carbon tetrachloride, and after its removal by filtration and evaporation, extracting fluid (0.5 per cent sodium chloride and 0.3 per cent sodium bicarbonate) was

*From the Department of Allergy, The Roosevelt Hospital, New York.

Presented in part before the meeting of the Society for the Study of Asthma and Allied Conditions, April 29, 1939, Atlantic City, N. J.

added to each in 500 c.c. amounts to give a thick mud consistency. Extraction was carried out under toluene for 24 hours at 7° C. The extracts were separated from the solid material in a meat press and dialyzed against running water under toluene for 24 hours. Five-tenths per cent sodium chloride and 0.3 per cent sodium bicarbonate were added, and the extracts were passed through Seitz filters and proved sterile by the usual cultural methods. A-dust was treated and extracted in the same way, except that a larger quantity of dust was used and phenol to 0.4 per cent concentration was added. No phenol was used in B-, C-, and D-dusts. All extracts were standardized[5] on a protein nitrogen basis* for use in the Dale tests (Table I). A portion of each of the four extracts was precipitated by the addition of alum (Al_2K_2 $(SO_4)_2.24H_2O$) to 0.5 per cent concentration, and the precipitates were centrifugalized, washed with 0.85 per cent sterile saline, and suspended in 0.85 per cent sterile saline. All these procedures were done with sterile precautions. The suspensions were analyzed for protein nitrogen by phosphotungstic acid precipitation (Table I) and were then used for sensitization of guinea pigs.

TABLE I

ANALYSES OF DUST EXTRACTS

SERIES	DUST EXTRACT	DATE OF PREPARATION	PROTEIN NITROGEN MG. PER C.C.	ALUM-PRECIPITATED SUSPENSION—PROTEIN NITROGEN MG. PER C.C.
A	A-dust	2/ 1/39	0.06	0.25
B	B-dust	4/12/39	0.11	0.40
C	C-dust	4/12/39	0.08	0.20
D	D-dust	4/12/39	0.04	0.15

Virgin female guinea pigs (250 to 300 gm. in weight) each received a single intra-abdominal injection of one of the purified alum-precipitated dust extracts. An amount containing 50,000 protein nitrogen units was injected into each animal. Dale tests were performed, following the technique described in the report of antigenic studies of pollen.[6] In the experiments with B-, C-, and D-dust extracts the two uterine horns were tested simultaneously.

The action of inhalants upon the dust-sensitive uterine muscles was studied in several guinea pigs in each series by testing the uterine horns with the common inhalant extracts in the order and strength listed in the protocols.†

The inhalant extracts used for testing were the routine extracts prepared and standardized on a protein nitrogen unit.[5, 7] In addition, human dander was collected from hair combings and was similarly extracted and standardized. It contained 13,000 units per cubic centimeter.

*1 unit = 0.00001 mg. protein nitrogen.

†Due to lack of space for publication, only Protocol 1, Series A, and part of Protocol 2, Series B, are given in this article.

In most instances half the group of inhalants were tested upon one horn and half upon the other, in varying strengths as indicated in Protocol 1, Series A, and the part of Protocol 2, Series B. When a reaction was obtained with an inhalant, however, the other uterine horn was usually tested with that particular inhalant as well.

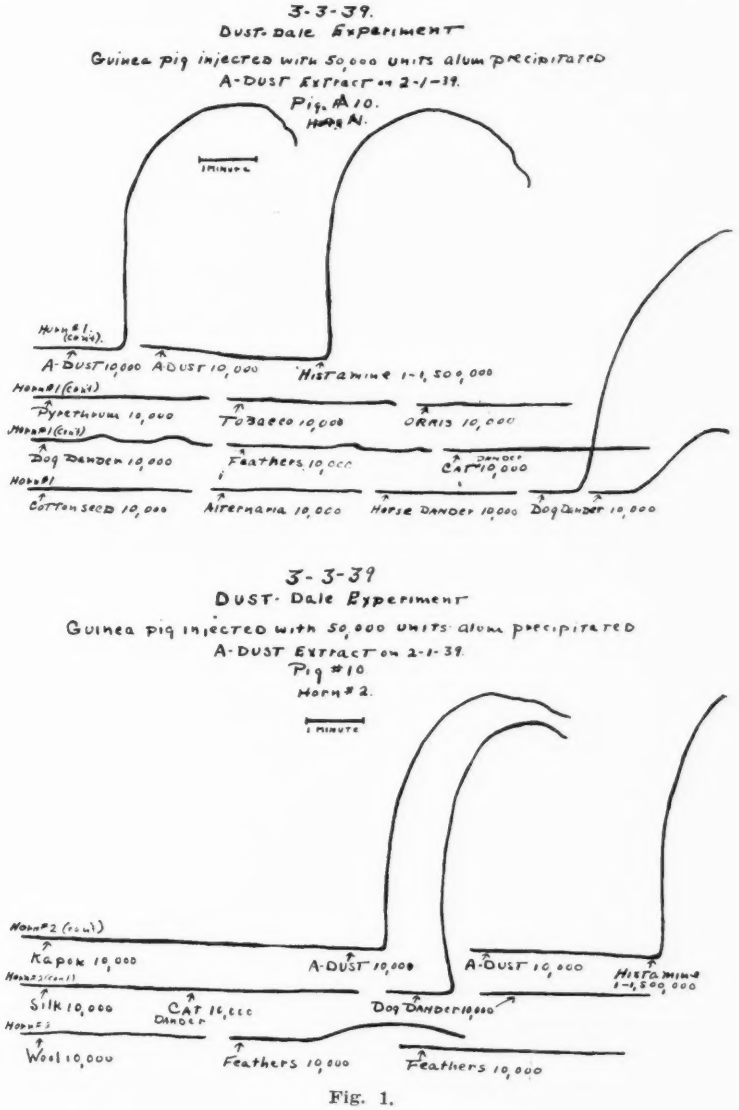

Fig. 1.

In the remaining guinea pigs, B-, C-, and D-dust extracts were tested in equal strengths for their capacity to cross-neutralize uteri from pigs sensitized to these dusts. In the cross-neutralization experiments the muscle was finally tested with a total of 30,000 units of the

sensitizing extract, after it had been shown to be neutralized to 10,000 units of a different dust extract.

A-dust was considered to contain all antigens common to house dust since it was prepared from dust from so many different sources. The guinea pigs in series A (sensitizing antigen, A-dust) were tested first, and since they failed to show sensitivity to cottonseed, pyrethrum, tobacco, orris, silk, wool, horse dander, *Alternaria*, ragweed, kapok, and cotton linters, these inhalant extracts were tested upon only a few of the uterine muscles in series B, C, and D. Those inhalants, namely, dog and cat dander and feathers,* which did produce positive reaction in series A, however, were tested in series B (sensitizing antigen, B-dust), series C (sensitizing antigen, C-dust), and series D (sensitizing antigen, D-dust), except when the observations were limited to cross relationship of the dust extracts. Furthermore, in series B, C, and D, human dander extract and seven mold extracts *(Alternaria, Monilia albicans, Mucor, Aspergillus, Hormodendrum, Penicillium,* and *Dematium)* were tested. Glue and jute extracts were tested in a few experiments.

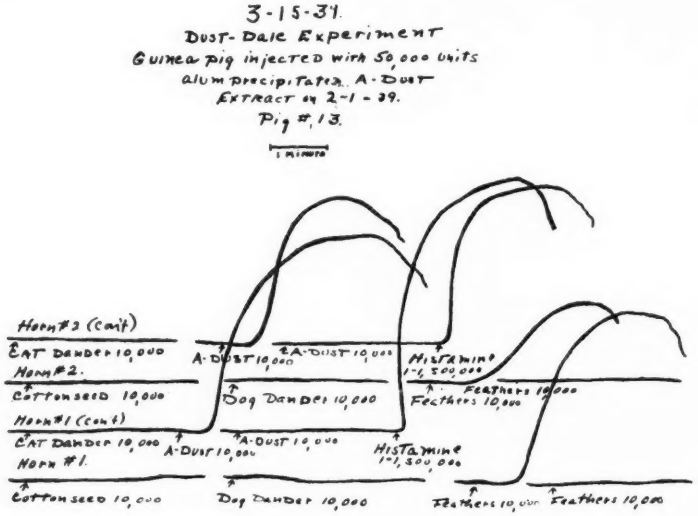

Fig. 2.

RESULTS

Series A. Sensitizing Antigen, A-Dust. (Protocol 1 and Table II.)—All of the ten guinea pigs in this group were found sensitive by the Dale test. Six of the eight uteri tested with feather extract gave positive reactions. Three of the ten uteri tested with dog dander extract gave positive reactions; four of the ten uteri tested with cat dander gave positive reactions. These findings are illustrated in the reproductions of the Dale curves (Figs. 1, 2, and 3).

*Mixture of chicken, duck, and goose feathers.

In seven of nine experiments in which reactions were obtained to one or more inhalants, the muscle reacted to dust extract after becoming neutral to the reacting inhalants (Figs. 1 and 2). The muscle failed to react in two experiments, suggesting that the inhalants

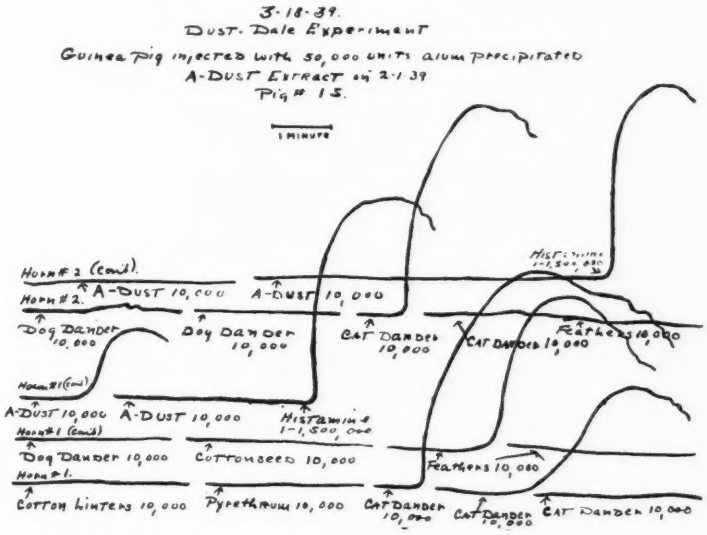

Fig. 3.

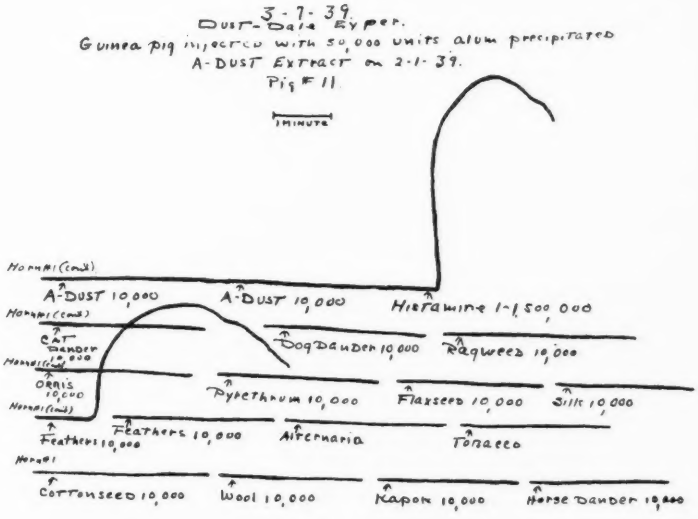

Fig. 4.

neutralized the uterine antibodies to dust (Fig. 4). In one instance, the horns of the uterus failed to react to all inhalants tested, but one reacted to the test with the sensitizing dust (guinea pig 7).

In the tests of guinea pigs 8 and 12, a fifth dust (No. 21639) obtained from a single source was used. This dust extract produced a

PROTOCOL 1. SERIES A

GUINEA PIGS INJECTED WITH 50,000 UNITS OF ALUM-PRECIPITATED A-DUST EXTRACT ON FEB. 1, 1939

GUINEA PIG NO.	UTERINE HORN	DATE TESTED	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
6	1	3/ 1/39	Ragweed	10,000	0
			Cottonseed	10,000	0
			Kapok	10,000	0
			Orris	10,000	0
			Pyrethrum	10,000	0
			Tobacco	10,000	0
			Silk	10,000	0
			Wool	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	0
			A-dust	10,000	0
			A-dust	20,000	0
			Histamine*		++++
	2		Cat dander	10,000	+++
			Cat dander	10,000	0
			A-dust	10,000	+++
			A-dust	10,000	0
			Histamine		+++
7	1	3/ 1/39	Cottonseed	10,000	0
			Kapok	10,000	0
			Orris	10,000	0
			Pyrethrum	10,000	0
			Tobacco	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	0
			Silk	2,500	0
			Wool	5,000	0
			A-dust	10,000	0
			Histamine		++++
	2		Cat dander	10,000	0
			Cat dander	10,000	0
			A-dust	10,000	++++
			A-dust	10,000	0
			Histamine		++++
8	1	3/ 1/39	Cottonseed	10,000	0
			Kapok	10,000	0
			Orris	10,000	0
			Pyrethrum	10,000	0
			Tobacco	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	+
			Cat dander	10,000	++++
			Cat dander	10,000	++
			Cat dander	10,000	±
			Cat dander	10,000	0
			A-dust	10,000	0
			Histamine		++++

*Histamine, 1:1,500,000.

PROTOCOL 1. SERIES A—CONT'D

GUINEA PIG NO.	UTERINE HORN	DATE TESTED	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
8	2	3/ 1/39	Low Ragweed	10,000	0
			Alternaria	10,000	0
			Silk	2,500	0
			Feathers	10,000	0
			Horse dander	10,000	0
			Dog dander	10,000	0
			Dust no. 21639	1 c.c.	0
			A-dust	10,000	0
			Cat dander	10,000	0
			Histamine		+ + + +
9	1	3/ 2/39	Silk	2,500	0
			Kapok	10,000	0
			Orris	10,000	0
			Dog dander	10,000	+ +
			Dog dander	10,000	0
			A-dust	10,000	+ + + +
			A-dust	10,000	+
			A-dust	10,000	+
			A-dust	10,000	0
			Histamine		+ + + +
	2		Feathers	10,000	+ + +
			Feathers	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	+ +
			Cat dander	10,000	0
			A-dust	10,000	+ + +
			A-dust	10,000	0
			Histamine		+ + +
10 (See Fig. 1.)	1	3/ 3/39	Cottonseed	10,000	0
			Alternaria	10,000	0
			Horse dander	10,000	0
			Dog dander	10,000	+ + + +
			Dog dander	10,000	+
			Dog dander	10,000	0
			Feathers	10,000	0
			Cat dander	10,000	0
			Pyrethrum	10,000	0
			Tobacco	10,000	0
			Orris	10,000	0
			A-dust	10,000	+ + + +
			A-dust	10,000	0
			Histamine		+ + + +
	2		Wool	10,000	0
			Feathers	10,000	+
			Feathers	10,000	0
			Silk	10,000	0
			Cat dander	10,000	0
			Dog dander	10,000	+ + + +
			Dog dander	10,000	0
			Kapok	10,000	0
			A-dust	10,000	+ + + +
			A-dust	10,000	0
			Histamine		+ + + +

PROTOCOL 1. SERIES A—CONT'D

GUINEA PIG NO.	UTERINE HORN	DATE TESTED	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
11 (See Fig. 4.)	1	3/ 7/39	Cottonseed	10,000	0
			Wool	10,000	0
			Kapok	10,000	0
			Horse dander	10,000	0
			Feathers	10,000	+++
			Feathers	10,000	0
			Alternaria	10,000	0
			Tobacco	10,000	0
			Pyrethrum	10,000	0
			Flaxseed	10,000	0
			Silk	10,000	0
			Cat dander	10,000	0
			Dog dander	10,000	0
			Ragweed	10,000	0
			A-dust	10,000	0
			A-dust	10,000	0
			Histamine		+++
	2		Cat dander	10,000	0
			Dog dander	10,000	0
			Cottonseed	10,000	0
			Alternaria	10,000	0
			Tobacco	10,000	0
			Orris	10,000	0
			Pyrethrum	10,000	0
			Silk	10,000	0
			Ragweed	10,000	0
			Feathers	10,000	0
			A-dust	10,000	0
			A-dust	10,000	0
			Alternaria	10,000	0
			Histamine		++++
12	1	3/ 9/39	Cottonseed	10,000	0
			Wool	10,000	0
			Alternaria	10,000	0
			Horse dander	10,000	0
			Feathers	10,000	++++
			Feathers	10,000	0
			Cat dander	10,000	+
			Cat dander	10,000	0
			Dog dander	10,000	0
			Silk	10,000	0
			Kapok	10,000	0
			Tobacco	10,000	0
			Orris	10,000	0
			Pyrethrum	10,000	0
			Ragweed	10,000	0
			Dust No. 21639	1 c.c.	+
			Dust No. 21639	1 c.c.	0
			A-dust	10,000	0
			Histamine		+++
	2		A-dust	10,000	++
			A-dust	10,000	0
			Feathers	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	0
			Dust No. 21639	1 c.c.	0
			Histamine		+++

PROTOCOL 1. SERIES A—CONT'D

GUINEA PIG NO.	UTERINE HORN	DATE TESTED	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
13 (See Fig. 2.)	1	3/15/39	Cottonseed	10,000	0
			Dog dander	10,000	0
			Feathers	10,000	+++
			Feathers	10,000	0
			Cat dander	10,000	0
			A-dust	10,000	++++
			A-dust	10,000	0
			Histamine		++++
	2		Cottonseed	10,000	0
			Dog dander	10,000	0
			Feathers	10,000	+
			Feathers	10,000	0
			Cat dander	10,000	0
			A-dust	10,000	+++
			A-dust	10,000	0
			Histamine		+++
14	1	3/17/39	Cotton linters	3,000	0
			Kapok	10,000	0
			Dog dander	10,000	+
			Dog dander	10,000	0
			Cat dander	10,000	0
			Feathers	10,000	0
			A-dust	10,000	++++
			A-dust	10,000	0
			Histamine		++++
	2		Cat dander	10,000	0
			Feathers	10,000	0
			Dog dander	10,000	0
			Dog dander	10,000	0
			A-dust	10,000	++++
			A-dust	10,000	0
			Histamine		++++
15 (See Fig. 3.)	1	3/18/39	Cotton linters	10,000	0
			Pyrethrum	10,000	0
			Cat dander	10,000	++++
			Cat dander	10,000	++
			Cat dander	10,000	0
			Dog dander	10,000	0
			Cottonseed	10,000	0
			Feathers	10,000	+++
			Feathers	10,000	0
			A-dust	10,000	+
			A-dust	10,000	0
			Histamine		++++
	2		Dog dander	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	++++
			Cat dander	10,000	0
			Feathers	10,000	0
			A-dust	10,000	0
			A-dust	10,000	0
			Histamine		++++

TABLE II

SUMMARY OF REACTIONS OF SERIES A

GUINEA PIGS INJECTED WITH 50,000 UNITS ALUM-PRECIPITATED DUST EXTRACT

TESTING ANTIGEN 10,000 UNITS	NO. OF UTERI TESTED	NO. OF POSITIVE REACTIONS
Dog dander	10	3
Cat dander	10	4
Feathers	8	6
Cottonseed	8	0
Pyrethrum	7	0
Tobacco	6	0
Orris	7	0
Silk, 2,500 and 10,000 Units	7	0
Wool	5	0
Horse dander	4	0
Alternaria	4	0
Ragweed	4	0
Kapok	8	0
Cotton linters, 3,000 and 10,000	2	0
Flaxseed	1	0
A-dust	10	7

reaction after the muscle was neutral to reacting inhalants and cross-neutralized with A-dust in one instance (guinea pig 12).

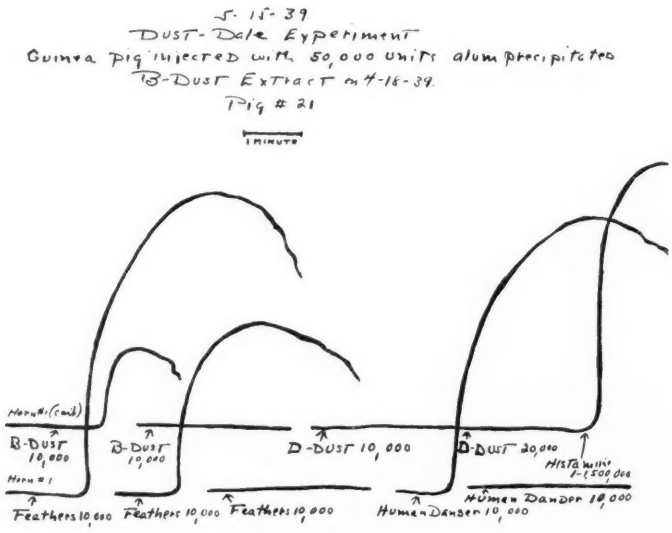

Fig. 5.

Series B. Sensitizing Antigen, B-Dust. (Protocol 2 and Table III.)—Six of the seven guinea pigs in this series were found sensitive by the Dale test. One of the four uteri tested with feather extract gave a positive reaction (Fig. 5). Dog and cat dander extracts failed to produce contractions. All of the four uteri tested with human dander extract gave positive reactions (Fig. 6).

In three of the four experiments in which reactions were obtained to one or more inhalants, the muscle reacted to a dust extract after it was neutral to the reacting inhalants, although the dust reactions were small and obtained upon only one horn in two instances (Figs. 5 and 6).

C-dust and D-dust extracts produced a contraction and neutralized the uterine muscle to B-dust extract (sensitizing antigen) in two cross-neutralization experiments (Figs. 7 and 8).

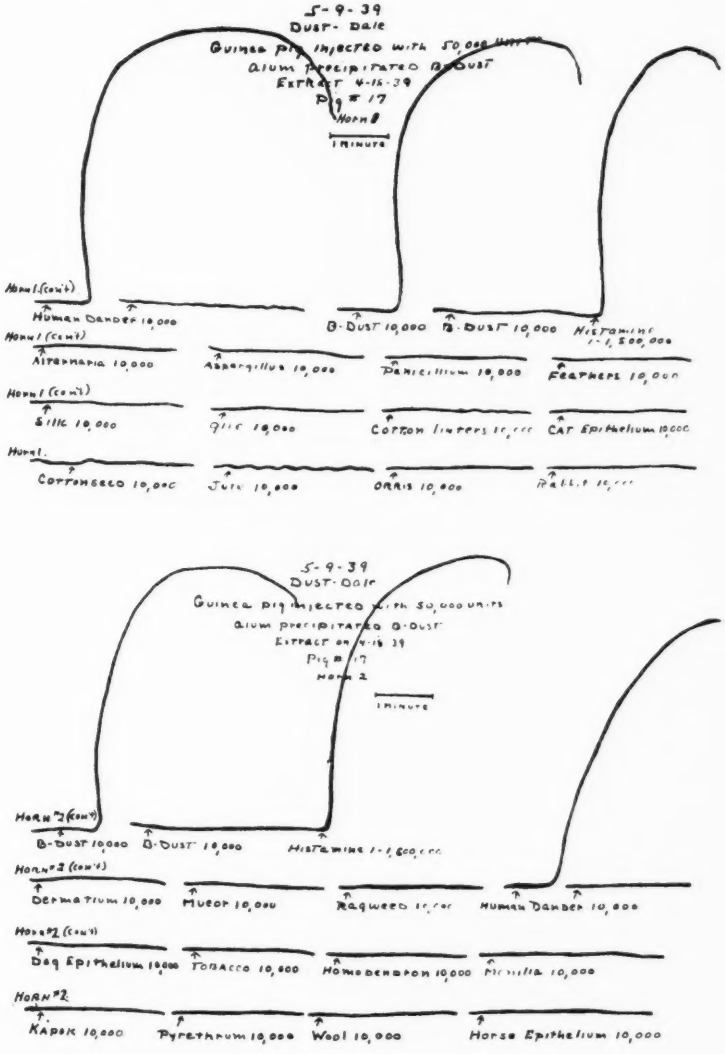

Fig. 6.

Series C. Sensitizing Antigen, C-Dust. (Table IV.)—Five of the seven guinea pigs in this series were found sensitive by the Dale test. One of the three uteri tested with dog dander extract gave a positive

PROTOCOL 2. SERIES B

GUINEA PIGS INJECTED WITH 50,000 UNITS ALUM-PRECIPITATED B-DUST EXTRACT ON APRIL 18, 1939

GUINEA PIG NO.	UTERINE HORN	DATE TESTED	TESTING ANTIGEN	PROTEIN NITROGEN UNITS	UTERINE CONTRACTION
24	1	5/18/39	Feathers	10,000	0
			Dog dander	10,000	0
			Cat dander	10,000	0
			Human dander	10,000	++++
			Human dander	10,000	+++
			Human dander	10,000	0
			C-Dust	10,000	0
			C-Dust	20,000	0
			B-dust	10,000	0
			B-dust	20,000	0
			Histamine		++++
	2		B-dust	10,000	++
			B-dust	10,000	++
			B-dust	10,000	+
			B-dust	10,000	0
			Human dander	10,000	0
			Cat dander	10,000	0
			Dog dander	10,000	0
			Feathers	10,000	0
			C-Dust	10,000	0
			C-Dust	20,000	0
			Histamine		+++
30 (See Fig. 7.)	1	5/28/39	D-dust	10,000	++++
			D-dust	10,000	0
			B-dust	10,000	0
			B-dust	20,000	0
			Histamine		++++
	2		B-dust	10,000	++++
			B-dust	10,000	0
			D-dust	10,000	0
			D-dust	20,000	0
			Histamine		++++
28 (See Fig. 8.)	1	5/25/39	C-dust	10,000	+++
			C-Dust	10,000	+
			C-Dust	10,000	0
			B-dust	10,000	0
			B-dust	20,000	0
			Histamine		+++
	2		B-dust	10,000	+++
			B-dust	10,000	+
			B-dust	10,000	0
			C-Dust	10,000	0
			C-Dust	20,000	0
			Histamine		+++

reaction (Fig. 9). Feathers and cat dander extracts failed to produce contractions. One of the four uteri tested with human dander gave a positive reaction (Fig. 10). In the two experiments in which reactions were obtained with inhalants, one of the uteri reacted to dust extract (Fig. 10) and one (guinea pig 22) did not react to dust extract after it was neutral to the reacting inhalant.

TABLE III

SUMMARY OF REACTIONS OF SERIES B

GUINEA PIGS INJECTED WITH 50,000 UNITS ALUM-PRECIPITATED B-DUST EXTRACT

TESTING ANTIGEN 10,000 UNITS	NO. OF UTERI TESTED	NO. OF POSITIVE REACTIONS
Feathers	4	1
Cat dander	3	0
Dog dander	3	0
Human dander	4	4
Cottonseed	2	0
Kapok	2	0
Orris	2	0
Horse dander	2	0
Pyrethrum	2	0
Tobacco	2	0
Silk	2	0
Wool	2	0
Alternaria	2	0
Monilia albicans	2	0
Mucor	2	0
Aspergillus	2	0
Hormodendrum	2	0
Penicillium	2	0
Dematium	2	0
Ragweed	2	0
Cotton linters	2	0
Glue	2	0
Jute*	1	0
B-dust	7	7
C-dust	3	1
D-dust	2	1

*Jute contained too small a quantity of protein for analyses. Testing strength 1 c.c.

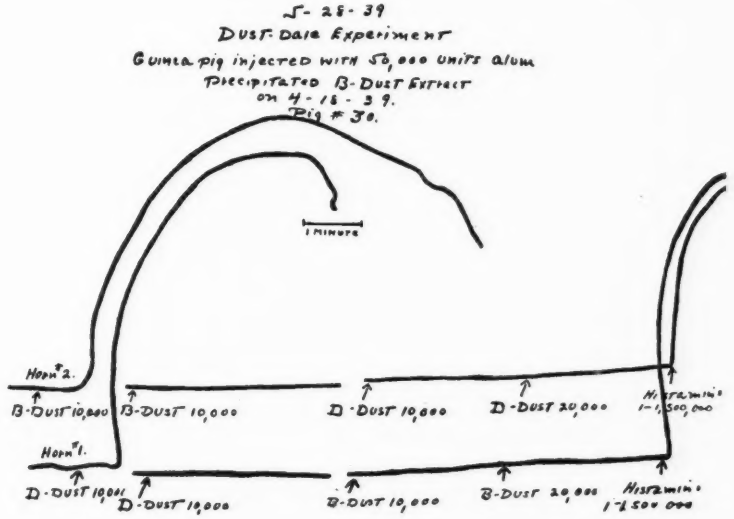

Fig. 7.

B-dust produced a contraction and neutralized the uterine muscle to C-dust (sensitizing antigen) in three experiments (Fig. 11).

Series D. Sensitizing Antigen, D-Dust. (Table V).—All seven pigs in this series were found sensitive by the Dale test.

Three of the four uteri tested with feather extract gave positive reactions (Fig. 12). No reactions were obtained with cat and dog dander extracts. Three of the four uteri tested with human dander gave positive reactions (Fig. 13).

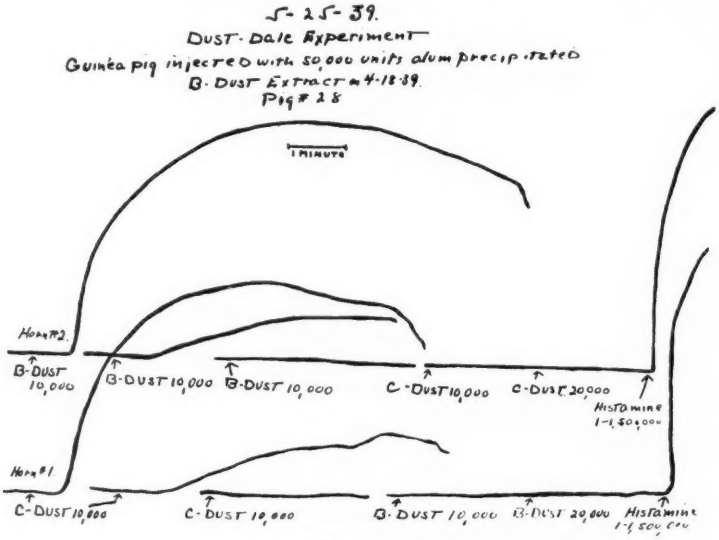

Fig. 8.

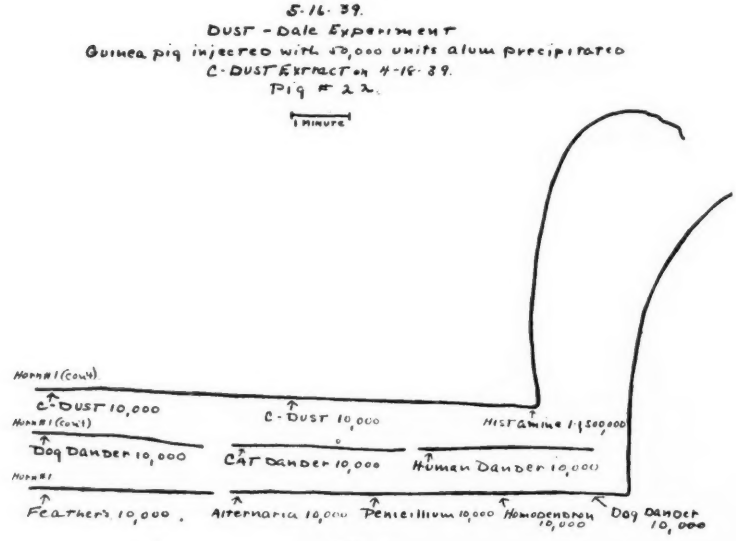

Fig. 9.

In two of the three experiments in which reactions were obtained with inhalants, the muscle reacted to dust extract after it was neutral to the respective inhalants (Figs. 12 and 13). One uterine muscle reacted to the sensitizing dust but to none of the inhalants tested.

TABLE IV

SUMMARY OF REACTIONS OF SERIES C

GUINEA PIGS INJECTED WITH 50,000 UNITS ALUM-PRECIPITATED C-DUST EXTRACT

TESTING ANTIGEN (10,000 UNITS)	NO. OF UTERI TESTED	NO. OF POSITIVE REACTIONS
Feathers	4	0
Cat dander	3	0
Dog dander	3	1
Human dander	4	1
Cottonseed	1	0
Orris	1	0
Horse dander	0	0
Pyrethrum	0	0
Tobacco	0	0
Silk	1	0
Wool	1	0
Alternaria	2	0
Monilia albicans	1	0
Mucor	1	0
Aspergillus	2	0
Hormodendrum	1	0
Penicillium	2	0
Dematium	1	0
Ragweed	0	0
Cotton linters	0	0
Glue	0	0
Jute*	1	0
C-dust	5	3
B-dust	3	3
D-dust	1	1

*Jute contained too small a quantity of protein for analyses. Testing strength 1 c.c.

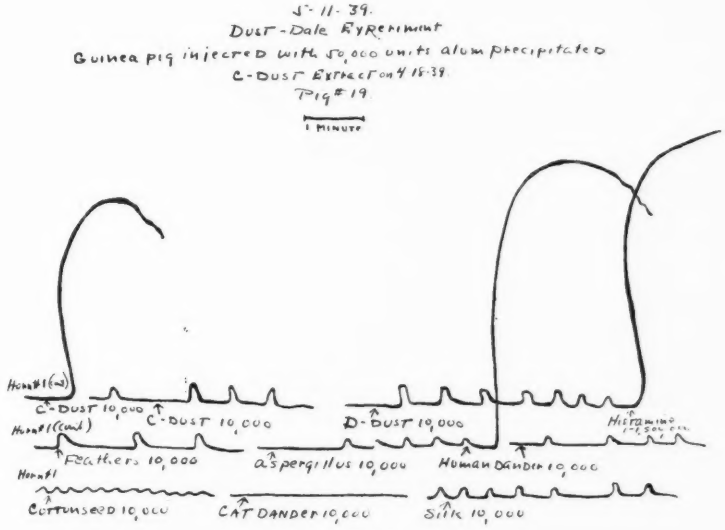

Fig. 10.

C-dust extract produced a contraction and neutralized the uterine muscle to D-dust extract (sensitizing antigen) in two experiments (Fig. 14). B-Dust extract produced a contraction and neutralized to D-dust extract in one experiment (Fig. 15).

DISCUSSION

Human dander, although one of the antigens for guinea pigs in house dust, was not the only antigenic factor in dust extract other than the common inhalants, since, in four of the five experiments in

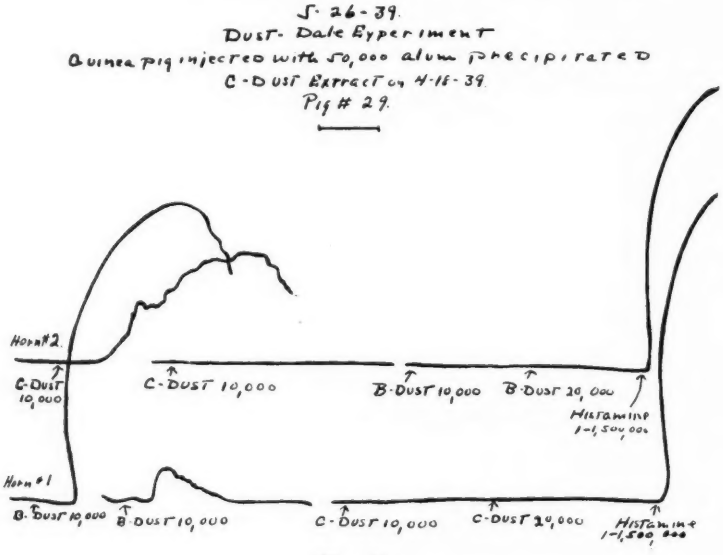

Fig. 11.

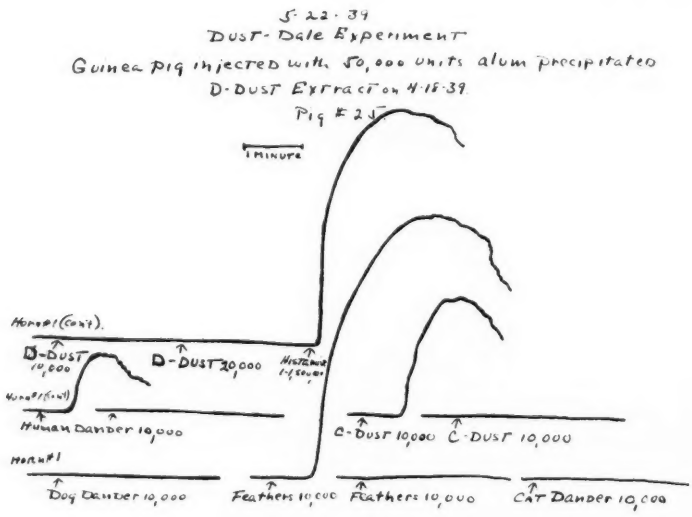

Fig. 12.

which human dander was the only inhalant causing muscular contraction, dust extract produced a contraction after the muscle was shown to be neutralized to human dander. There was no evidence of a histamine-like substance in the human dander extract or the dust extracts.

In order to determine that human dander was antigenic for guinea pigs, 50,000 units of alum-precipitated suspension of human dander were injected into each of four guinea pigs. The uteri of two guinea pigs were reactive to the dander extract. B-dust produced a positive reaction in the only instance in which it was tested on a uterine muscle, sensitive to human dander, but it did not completely neutralize to this dander extract in 10,000 unit strength (Fig. 16).

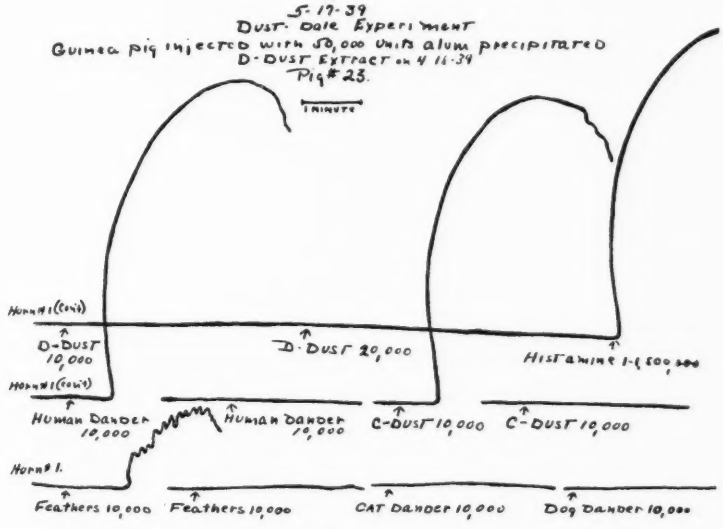

Fig. 13.

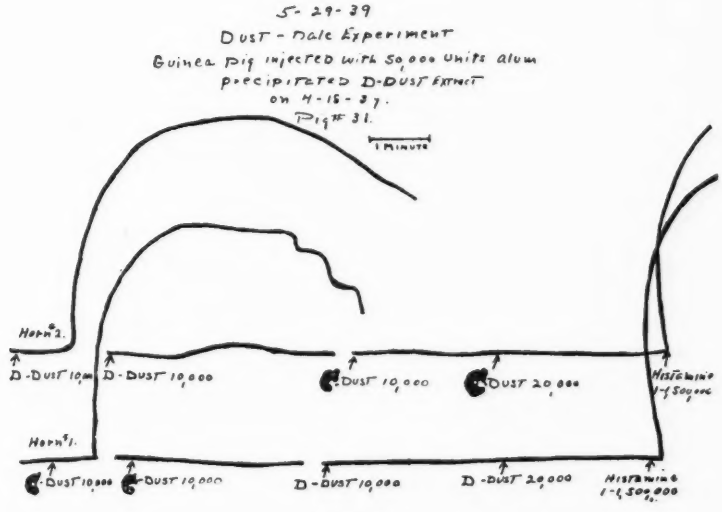

Fig. 14.

In the experiments in which a different dust extract produced a reaction prior to testing with the sensitizing dust extract, the uterine

TABLE V

SUMMARY OF REACTIONS OF SERIES D

GUINEA PIGS INJECTED WITH 50,000 UNITS ALUM-PRECIPITATED D-DUST EXTRACT

TESTING ANTIGEN (10,000 UNITS)	NO. OF UTERI TESTED	NO. OF POSITIVE REACTIONS
Feathers	4	3
Cat dander	4	0
Dog dander	4	0
Human dander	5	3
Cottonseed	2	0
Kapok	1	0
Orris	1	0
Horse dander	1	0
Pyrethrum	1	0
Tobacco	1	0
Silk	1	0
Wool	1	0
Alternaria	2	0
Monilia albicans	1	0
Mucor	1	0
Aspergillus	1	0
Hormodendrum	1	0
Penicillium	1	0
Dematium	0	0
Ragweed	1	0
Cotton linters	1	0
Glue	1	0
Jute*	1	0
D-dust	7	4
C-dust	5	4
B-dust	2	2

*Jute contained too small a quantity of protein for analyses. Testing strength 1 c.c.

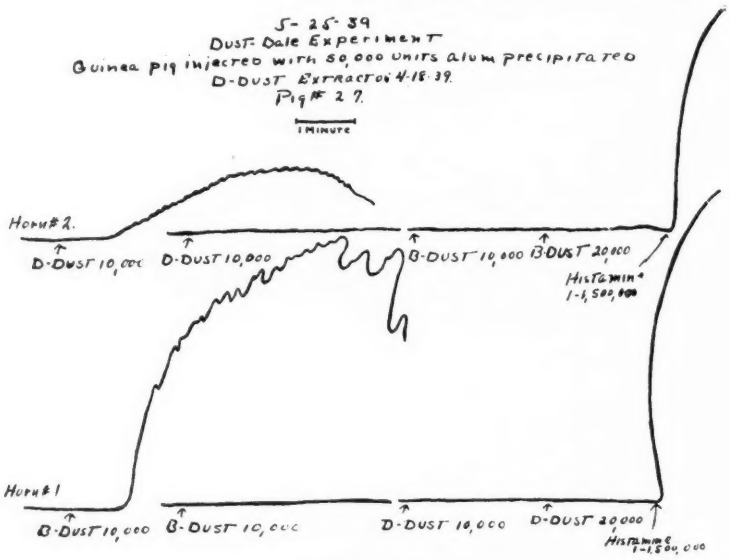

Fig. 15.

muscle was completely neutralized in all of twelve instances to the sensitizing dust. Six of this group were straight cross-neutralization experiments.

In the experiments in which the sensitizing dust extract produced a reaction prior to testing with another dust extract, the uterine muscle was completely neutralized in twelve of thirteen instances to another dust. Six were straight cross-neutralization experiments. In one experiment (guinea pig 23) in which a uterine horn was sensitized by D-dust extract, C-dust extract produced a small contraction after the muscle was shown to be neutralized to D-dust.

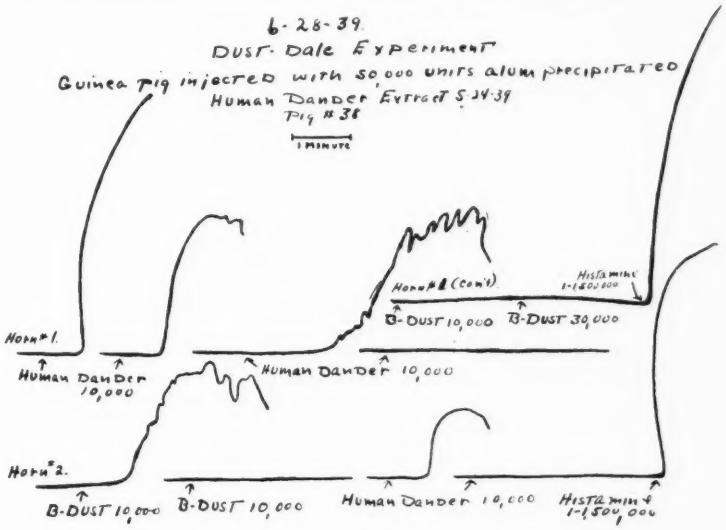

Fig. 16.

In carrying out Dale tests in the past, using antigens other than dust, it has been an unusual occurrence for one uterine horn to be sensitive and the other insensitive. It must be pointed out, however, that in this study with house dust, the two uterine horns frequently failed to respond alike. For examples, in series A, horn No. 1 of guinea pig 15 (Fig. 3) reacted to feathers while horn No. 2 did not, and horn No. 2 of guinea pig 7 reacted to dust extract while horn No. 1 failed to react, although in each instance the horns gave the normal response to histamine.

In fact, in series A, in six of the ten experiments, the two uterine horns of the respective guinea pigs failed to react similarly. This was the case in series B, C, and D (guinea pig 33) in a small number of instances. However, the respective horns were not previously tested with exactly the same inhalant antigens. It is interesting to note that the two horns reacted similarly in the cross-neutralization experiments in which only dust extracts were used. This suggested that the dust extracts might contain minute quantities of various inhalant antigens, and, although the inhalants themselves did not produce a muscular contraction, they may have neutralized the smooth

muscle antibodies. Consequently, the failure of dust extract to produce a contraction may have been due to the accumulative neutralizing activity of the several inhalants. This might suggest that the only antigens in dust extract were the inhalants which were tested. That this was not true, however, was shown by the many experiments in which dust extract produced positive Dale tests after the uterine muscle was shown to be neutralized to the reacting inhalants. On the other hand, it is possible that inhalant extracts contain traces of house dust, and it may thus be the accumulative effect of the dust factor in the various inhalants that brings about neutralization without producing contractions.

The presence of 0.4 per cent phenol in the inhalant extracts was another possible cause of inhibiting reactions after multiple tests. This was very unlikely in view of the many instances in which the muscles were tested with many inhalants and subsequently reacted to dust extract as well as to histamine.

One might assume that multiple sensitization occurred with such a composite antigen as house dust, but why, in some instances, one horn was found sensitized to one antigen, while the other horn was apparently sensitized to a different one, is not explained in the present study.

The "nonspecific toxic factor" producing anaphylactoid symptoms in gross anaphylaxis, described by Coulson and Stevens, was not observed in these experiments in which the Dale test was used. However, their extracts were not said to be dialyzed, whereas the extracts used in this study were dialyzed.

Precipitin tests were performed with the dust extract used for sensitization in sera from guinea pigs 25 (D-dust), 27 (D-dust), 22 (C-dust), 26 (C-dust), 21 (B-dust), and 28 (B-dust), and the sera failed to show precipitins.

SUMMARY

Twenty-eight of 31 guinea pigs, given a single intraperitoneal injection of purified alum-precipitated house dust extract from four different sources, were found sensitive by the Dale test.

Positive Dale tests were obtained with feather extract in 10 of 20 experiments, with dog dander in 4 of 20 experiments, and with cat dander in 4 of 20 experiments.

Cottonseed, cotton linters, kapok, raw silk, orris, glue, pyrethrum, wool, tobacco, ragweed, jute, horse dander, and the molds, *Alternaria*, *Aspergillus*, *Mucor*, *Monilia albicans*, *Dematium*, *Penicillium*, and *Hormodendrum*, failed to produce positive Dale tests in a total of 147 tests on dust-sensitized guinea pigs.

Uterine muscles, sensitized by dust extract, gave positive Dale reactions to dust extracts after the muscles were neutralized to certain reacting inhalants in 13 of 18 instances.

With the use of 3 dust extracts, 2 prepared with dusts from individual sources (B-dust and C-dust) and one from several sources (D-dust), neutralization to the sensitizing dust extract was effected by one or by the other two dusts in all of the 12 experiments. The sensitizing dust extract neutralized to one of the other dust extracts in 12 of 13 experiments.

Human dander extract gave a positive Dale test in 8 of 12 uteri sensitized by dust extract, but completely neutralized to dust extract in only one instance.

Alum-precipitated human dander extract sensitized 2 of 4 guinea pigs injected, and one of these two was sensitive to dust extract.

House dust extract contained an antigen other than that found in the known inhalants tested, and this antigen was common to three different dust extracts as determined by the Dale test.

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AN IONIC TRANSMISSION METHOD FOR TESTING WITH ALLERGENS*

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IT HAS long been thought that skin testing in allergy could be greatly improved by reducing the trauma associated with the pressure. An ideal method would be one requiring no mechanical injury. A hint to such a method of testing was a report by Abramson, Sookne, and Moyer.[1] They found that wheals could be produced with ragweed extract in persons hypersensitive to that pollen by electrophoresis, and could be obtained after five to ten minutes with current densities of 0.3 to 0.5 milliamperes. From the discussion incident to this report, it appeared that their interest in this subject was concerned primarily with certain theoretical considerations relative to the transport of negatively charged substances of high molecular weight. This suggested that the use of such a technique would, perhaps, offer a practical means of achieving routine skin testing without the undesirable traumatic effects of scratching or intradermal applications of extract.

A few simple tests with a galvanic current of 0.5 milliamperes and the conventional cotton pad electrodes speedily confirmed the observations of Abramson and his associates that wheals were readily produced with allergenic extracts.

Before reporting the practical results of such testing, it is of interest to review the theory of iontophoresis and electroosmosis. According to Abramson,[2] Abramson and Alley,[3] Abramson and Ochs,[4] and Harpuder,[5] theoretically, in iontophoresis only ionized material is carried by the electric current. In ideal systems, the velocity and the number of ions migrating in the electric field are predictable by formula. However, the introduction of the skin as a barrier alters the ideal conditions so that the ionic mobility and the number of ions must be changed. These changes are brought about because of varying dielectric constant, viscosity, and selective diffusion, and it has been demonstrated that these differences may result in values that fluctuate widely.

It is not possible to predicate the ionization of substances and the mobilization of such ions into the skin by means of an electric current on a simple basis. One must take into account the modifying effect of electroosmosis. Here we are dealing with the movement of streams of water through the pores of the skin when the skin and water systems are under the influence of a direct electrical current. The pores of the

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skin bear electric charges, and their isoelectric point is between pH 3 and 4. The pores of the skin being thus charged, undissociated substances may be moved by the electric forces. The electrically charged skin pore carries a definite electrokinetic potential. This is of the same nature as the electrokinetic potential of blood cells, bacteria, etc. Abramson states: "If we imagine the pores of the skin to act as a series of very fine tubes, the liquid in these tubes will move because of electro-osmosis to the negative pole in media alkaline to the iso-electric point of the pore surface." If the wall of the pore is effectively charged negatively, the liquid will be positively charged. Depending upon the sign of charge and current direction, electroosmosis would modify the iontophoretic transport by carrying undissociated substance in the moving stream of water. To illustrate: According to Abramson, "Let M-ion represent the quantity of a negatively charged ion carried by iontophoresis when the negative pole is applied, and M-o represent the quantity of undissociated substance moved by electro-osmosis. Then the total substance transported is M-ion plus M-o. If the skin is negatively charged and the negative pole is applied, the ions are driven into the skin, but the liquid in the pores of the skin carries, in addition, undissociated substance toward the negative pole so that it will be moved electro-osmotically out of the skin to the applied electrode. The sign M-o is therefore negative, and the total transport is M-ion minus M-o."

Abramson stated that he observed that the active constituents of extracts of ragweed and timothy pollen could be readily introduced by the galvanic current into the skin of sensitive individuals. The wheals formed were large and roughly comparable to those produced by intracutaneous injections. It was unexpectedly found that the negatively charged ragweed protein was usually more readily introduced by the positively charged pole. In this instance, presumably this difference was noted because movement of the protein due to ion mobility was less than that produced by electroosmosis.

Harpuder found from biopsies on human skin diffuse penetration of dyes through the rete Malpighii and a moderate migration along hair follicles and coil glands to subcutaneous fibers. The deeper structures remained unstained, even after applications of one hour. He, as well as Abramson, pointed out that electrolytic impurities may greatly impede electroosmotic migration and that the role of pH for electroosmosis is entirely different from its role in ionization. The skin carries normally, or when in contact with a solution of pH 4 or more, a negative charge, and electroosmosis takes place from the positive to the negative pole. Contrariwise, if the skin is in contact with solutions of a pH below 3, it becomes positively charged, and the fluid in its pores will, therefore, be negatively charged and migrate from the negative to the positive pole.

In view of these theoretical considerations, and in view of the meagerness of Abramson's statements concerning the production of ragweed wheals, a number of preliminary experiments were made with various allergenic extracts. The apparatus used for this work consisted of a simple battery of 15 volts with a voltage meter, milliammeter, and a simple rheostat in the positive lead. In our early work, the electrodes consisted of cotton pads. Underneath the positive pad, small pledgets of cotton, saturated with the allergen to be tested, were placed in contact with the skin. The current density was 0.5 milliamperes applied for ten minutes. Eight or ten allergens were tested at each sitting. It was found by this method that positive pollen tests were readily obtained. Tests for animal epidermals and house dust were less successful, and positive tests for foods were successful only on individuals who showed marked skin reactions by other methods. After investigating the effect of the area of the electrode, we found that much more intense reactions could be obtained with all classes of extracts when the area of the electrode was decreased to about 0.5 to 1.0 sq. cm. This, of course, decreased the practical effectiveness of any apparatus in regard to the number of tests it was possible to do at one time. At present we have constructed an apparatus having 10 positive leads by using two B batteries and a milliammeter and rheostat in each positive lead. We are thus able to deliver simultaneously comparable electric densities to 10 small areas. We have found this to be quite effective in testing with pollens, dusts, and foods.

The skin reactions obtained by this method are quite similar to those obtained by scratch or intradermal testing, with flushing surrounding a definite wheal. Sometimes there are multiple papular points in the center of the reddened area that do not coalesce. In control reactions and negative reactions there is no evidence whatsoever of change in the skin. We have, therefore, been led to adopt the tentative interpretation that reddening, without papule or wheal formation, is a weak positive reaction. Moreover, after testing a number of patients by this method, we were struck by the marked decrease in the number of positive reactions in certain individuals. Hence, gradually we have come to believe that tests by this method more closely parallel actual clinical sensitivity than do tests by other methods. To emphasize this point, we have selected the cases outlined in Table I because they had given a confusingly large number of positive reactions by ordinary skin tests. Also, all of them have been under observation and treatment for a sufficient period of time that their clinical sensitivities have been fairly well charted.

DISCUSSION

A study of these tables discloses that, in the main, the electroosmotic type of testing parallels clinical sensitivity much more closely than does scratch testing. Particularly is this so in individuals, of whom there

TABLE I

CASES ILLUSTRATING COMPARISON OF REACTIONS

SUMMER AND FALL HAY FEVER

HOUSE DUST CLINICALLY NEGATIVE

NO. 1. MR. C.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Arizona cottonwood	0	++++
Mulberry	+	++++
Careless weed	++++	++++
Sugar beet	++++	++++
House dust	0	++
Duck feathers	+++	+++
Flaxseed	0	++++
Cotton	0	++++

FALL HAY FEVER

NO. 2. H. A.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Mulberry	+	++++
Arizona cottonwood	0	++++
Arizona ash	+	++++
Western juniper	+	++++
Bermuda	++++	++
Russian thistle	++++	++++
Careless weed	+	++++
Salt bush	0	++++

ELM SEASON HAY FEVER

FALL HAY FEVER

NO. 3. MR. T.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Bermuda	+	++++
Arizona ash	0	++++
Arizona cottonwood	0	++++
Elm	++	++++
Shad scale	0	+++
Western ragweed	0	++++
Russian thistle	0	++++
Careless weed	++	++++

SUMMER AND FALL HAY FEVER

NEGATIVE CLINICAL SENSITIVITY TO HOUSE DUST, DOG HAIR, AND GOOSE FEATHERS

NO. 4. MRS. V.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Bermuda	++++	++++
Arizona ash	0	++++
Mountain cedar	0	++++
Russian thistle	++++	++++
Careless weed	++++	++++
House dust	0	++
Dog hair	0	+++
Goose feathers	0	+++

TABLE I—CONT'D

SUMMER AND FALL HAY FEVER

NONE IN MOUNTAIN CEDAR AREA

NO. 5. MR. W.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Bermuda	++++	++++
Mulberry	++	++++
Arizona cottonwood	+	++++
Elm	++++	++++
Russian thistle	++++	++++
Shad scale	+	++++
Careless weed	++++	++++
Alfalfa	++	++++
Mountain cedar	0	+++

FALL HAY FEVER AND ASTHMA

SYMPTOMS—CARELESS WEED SEASON

NO. 6. M. S.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Shad scale	0	+++
Annual salt bush	0	++++
Western ragweed	0	++
Russian thistle	0	++++
Careless weed	+++	++++
Rough pigweed	0	++++
Prostrate pigweed	+	++
Spring pigweed	0	++
Big burr salt bush	++	0
Bermuda	0	++

FALL HAY FEVER

NO. 7. MRS. T.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Bermuda	++++	++++
Arizona cottonwood	++	++++
Arizona ash	++++	++++
Mulberry	++	+++
Shad scale	+	++++
Russian thistle	++++	++
Careless weed	++	++
Western ragweed	++++	+++

CLINICALLY SENSITIVE TO WHEAT AND EGG ONLY

NO. 8. H. S.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Spinach	0	++
Wheat	++	0
Egg white	+++	++
Pork	0	+++
Banana	0	+++
Rice	0	++++
Corn	0	0
Lima bean	0	++++

TABLE I—CONT'D

CLINICALLY SENSITIVE TO MILK AND PINEAPPLE ONLY

NO. 9. MRS. T.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Milk—casein	++	0
Milk—albumin	?	0
Pineapple	++++	++++
Tomato	++	++++
Cauliflower	0	++++

SPRING AND FALL EXACERBATIONS OF PERENNIAL HAY FEVER

CLINICALLY SENSITIVE TO HOUSE DUST

NO. 10. MRS. J.

	SKIN REACTIONS	
	ELECTRO REACTION	SCRATCH REACTION
Bermuda	++++	+++
Arizona cottonwood	++++	++++
Elm	+?	++
Rabbit bush	++++	++++
Annual salt bush	++	++++
Russian thistle	++++	++++
Careless weed	++++	++++
House dust	++	++++

are many, who give large numbers of positive reactions to substances to which they are not clinically sensitive. It seems justifiable, therefore, to assume that, with more refined technique, such a type of testing would be of considerable practical value.

In connection with the technique, there are many problems yet to be solved. The most important probably centers around the type of extract to be used. As has been pointed out, the pH, the presence of electrolytes, and the concentration of the substances in solution, all have a highly important bearing on the production of sufficient mobility of the substance to insure that adequate amounts enter the skin. We have carried out a number of experiments, paralleling tests with the conventional glycerosaline extract with tests with simple aqueous extracts that have no added electrolytes or glycerin. It is unmistakable that with the aqueous extracts we obtained considerably more penetration as evidenced by the size of the resulting wheal. Furthermore, in many instances, we have been able to reduce the time of exposure from ten minutes to two or three minutes and yet obtain comparable wheal production. We have not yet been able to do comparative tests with extracts of different pH. It is most likely that when these are done, some considerable variation will be found.

It is probable that simple aqueous solutions of precipitated and dried protein will offer acceptable testing material by this method. To judge from the few experiments made with such extracts, they appear to be definitely superior to glycerosaline extracts. Whether or not this will

also be observed when compared with simple aqueous extracts of the whole food, is unknown. Likewise, more comparative data are needed with different current densities and time lengths of exposure.

In one instance, we attempted to increase gradually the size of the wheal by increasing both the time of exposure and the area of the skin. This was done in a patient who had definite asthmatic attacks from pollen. By this method, we reached a point where a mild systemic reaction took place following the production of a wheal about 3 cm. in diameter. It is obvious, therefore, that it is possible to control the amount of extract introduced by this process, and that sufficient quantity can be introduced to cause systemic absorption.

Obviously, a great many more comparative tests by this method must be done before its practical value can be determined. The small number of tests made prohibit the drawing of final conclusions relative to its merit. Likewise, it is obvious that much more work must be done on the technique of performing the tests and more studies carried out to determine the type of extract best suited for such testing. It is with these deficiencies in mind that this preliminary report is offered.

I wish to acknowledge the assistance of Dr. A. P. Black for his valuable suggestions in the course of these studies.

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DISCUSSION

DR. B. G. EFRON, New Orleans.—Contrary to everyone else's experience, certainly mine, Dr. Dutton gets a tremendous number of false positive scratch tests. I am sure that most of us who do scratch tests with present day extracts not only fail to bring out food sensitivity, but also that in the South and the Southeast particularly, there is a type of seasonal hay fever which invariably gives us a large number of false negative rather than a large number of false positive pollen reactions.

The last slide was very interesting to me because of the house dust reaction, in which the patient was sensitive to house dust and gave a two-plus reaction with the electrophoretic method and a four-plus reaction with the scratch test. These reactions, perhaps, give us a clue as to just what is going on; they show that the reason for the greater number of negative reactions with the electrophoretic method than with the scratch test is that, by the use of the electrophorectic method, a smaller amount, a subthreshold amount in most instances, of the antigen gets into the skin, and, hence, the reactions are smaller and in many cases negative.

DR. HARRY L. ALEXANDER, St. Louis.—Iontophoresis implies a dissociation into component parts of a salt or other chemical arrangement. Proteins do not dissociate very well; the molecule is far too big. I wonder if it is possible that none of these allergens ever got into the skin. If that is true, it may well be due to the fact that it is very difficult to dissociate proteins and drive the allergenic component of them into the skin. On the other hand, if these results are what they seem to be, I must say it is a very important contribution.

DR. DUTTON.—I have just a word to say in regard to what Dr. Efron has mentioned about the large number of false positive reactions. These were in a few selected patients who did give a large number of false positive reactions; in other words, I hope you do not feel that that is an index of the number of false positive reactions that we got on our whole series.

I am quite in agreement with the fact that we are getting less into the skin by this method than we are, possibly, by scratch testing, and certainly less than we are getting intradermally, but that might be advantageous at times.

Certainly the lack of trauma might cut down our false positive reactions. I did not get to dwell on that part of it.

In regard to Dr. Alexander's point, let me explain that, by means of electro-osmosis, it is not necessary to dissociate a substance carried into the skin by this method. It is possible to carry undissociated substances in a stream of positively charged water which flows through the pores of the skin.

SIGNIFICANCE OF COTTONSEED SENSITIVENESS*

HARRY S. BERNTON, M.D., JOSEPH R. SPIES, PH.D., AND HENRY STEVENS, PH.D., WASHINGTON, D. C.

IN A recent publication[1] we reported the isolation of a potent allergenic fraction from the water-soluble constituents of cottonseed embryo. By means of this fraction, CS-1, and a derivative, CS-1 picrate, it has been possible to classify the patients allegedly sensitive to cottonseed. Thus type I patients are those who react positively to cutaneous tests with whole cottonseed or unfractionated extracts of cottonseed and negatively to the purified fractions, CS-1 and CS-1 picrate, in any concentration. Antibodies for cottonseed have not been demonstrated in the sera of these type I patients.

Type II patients react positively, not only to unfractionated cottonseed, but also to high dilutions of CS-1 and CS-1 picrate. With one exception, antibodies for cottonseed have been demonstrated in sera from this group. Moreover, these type II patients manifest, by constitutional symptoms, a high degree of clinical sensitiveness to the purified fractions. The conclusion seems warranted, therefore, that cutaneous sensitiveness to CS-1 and CS-1 picrate signifies clinical sensitiveness to cottonseed.

The opinion has long prevailed that a positive skin reaction to diluted allergen extracts of cottonseed should be considered specific and significant. Even those who emphasize the fallibility of the cutaneous test have seemed inclined to concede, by exception, some real significance to the positive cottonseed reaction. Precisely what this reaction should signify to the allergist has been more often implied than defined. Invariably, attention is directed to the use of refined cottonseed oil for making shortenings, for salad and cooking oils, salad dressings, for frying or other culinary purposes. Other possible contacts with a wide array of inedible derivatives of cottonseed have been mentioned too often to require repetition. In attempting to determine which of these potential sources of cottonseed allergens are offenders, the allergist has been confronted with an exceedingly complex problem.

Refined cottonseed oil and plastic shortening made from it are the only important edible derivatives of cottonseed. These derivatives, among all products of the cottonseed, demand major consideration. This conclusion is based upon the fact that cottonseed furnishes an important proportion of the primary fats annually required for food.

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*Contribution from Allergen Investigations, Bureau of Chemistry and Soils, U. S. Department of Agriculture, and the Allergy Clinic of Providence Hospital, Washington, D. C.

Read before the Annual Meeting of the American Society for the Study of Allergy, St. Louis, Mo., May 16, 1939.

Moreover, edible cottonseed oil is for the most part consumed as an ingredient of foods which individually bear no specific designation concerning the origin of their component fats. A dietary regimen which would assure avoidance of cottonseed oil, if necessary, would prove restrictive to a degree not generally realized.

The primary aim of the studies described in this report was to determine whether the allergenic components of the cottonseed embryo could be detected in the refined edible cottonseed oil or in the hydrogenated oil. Information gained from earlier studies of the cottonseed and the availability of cottonseed derivatives of known identity and history permitted refinements in procedures which have not been possible hitherto. Five type II patients selected for this study are in every respect representative of allergic subjects who would be judged by every available criterion to be clinically sensitive to cottonseed.

Two representative edible products of cottonseed were chosen for this investigation. The cottonseed oil selected was of established identity and purity, and conformed to the specifications for cottonseed oil U.S.P. This is an edible oil, but it is not as extensively processed as cottonseed salad oils generally available to the retail buyer. The hydrogenated oil employed in this study was representative of the hydrogenated cottonseed oil widely used in this country for the manufacture of shortening and cooking fats. In our use the hydrogenated cottonseed oil was colored and salted slightly to improve its acceptability for ingestion trials when relatively large quantities were fed.

The first attempt to detect cottonseed allergen in the refined oil was by an extraction process designed to separate and concentrate any water-soluble material in suspension or solution in the oil. The oil was expelled from a capillary tube into water. The apparatus allowed tiny droplets of oil to rise gradually through a narrow column of water, 58 cm. in length. The extraction was continued until 3,000 ml. of oil had passed twice through 100 ml. of water. This water extract was then concentrated in a vacuum over phosphorus pentoxide to a volume of 15 ml. The concentrated water extract was analyzed by the Kjeldahl micromethod. No nitrogen was found. No nitrogen was detected in the original oil when tested for this element by the method of Baker and Barkenbus.[2]

Both cutaneous and intracutaneous tests were performed with the water extract on four of our type II patients, with negative results. Two recipients were sensitized with a cottonseed serum of high titer. The two passively sensitized sites yielded negative results when tested with the concentrated water extract of the oil. Furthermore, cutaneous tests with the oil, performed on the same subjects, proved negative. Patch tests with the oil, on unbroken and scratched areas of skin, revealed no evidence of irritation at the end of forty-eight hours.

The mucous membrane of the conjunctival sacs and of the nasal passages was also subjected to the action of the cottonseed oil. Two drops of the warm oil were instilled into the conjunctival sac, and the eye was kept closed for five minutes. Observation of the patient was continued for one-half hour. There was no evidence of congestion or lacrimation, nor was there any complaint of itching for forty-eight hours ensuing.

The response of the upper respiratory tract to the action of the oil was next studied. First, 0.5 ml. of the warm oil was instilled into each nostril. This volume was increased to 1 ml. in subsequent trials. The head was maintained in the Parkinson modification of the Proetz position for five minutes. Very slight drainage occurred immediately after the resumption of the upright position. The youngest patient, aged 12 years, gave two single sneezes in the course of ten minutes. Paroxysmal sneezing, coryza, and itching were absent. No changes in the nasal mucosa were detected by direct examination. Observation of each patient was continued for one-half to one hour. No constitutional symptoms were reported at a later time. It is noteworthy that two series of these instillation experiments with the oil were performed in each of 3 patients very sensitive to cottonseed allergen.

Ingestion studies with cottonseed oil and with the hydrogenated cottonseed oil assume a special significance. Allergic symptoms are generally attributed to these foods if the patient exhibits a positive reaction to cottonseed. The effects of the oral administration of cottonseed oil to 5 of our type II patients were studied. Three of the patients have been under continual supervision for the past two years, one patient for four months, and the fifth patient has reported occasionally since the beginning of the present investigations. Doses varying from ¼ teaspoonful to 3 tablespoonfuls of the oil were administered by mouth to these patients at the clinic. When ten or more administered doses initiated neither immediate nor delayed allergic symptoms, the oil was dispensed to the patients. According to directions, 2 or 3 tablespoonfuls were taken daily. Records of the patients' condition during these ingestion trials were based on information gained by questioning and by clinical observations at frequent intervals. Quantities of cottonseed oil dispensed to 5 patients were, respectively, 100, 150, 200, 500, and 500 ml. In addition, 3 patients were given saltine crackers, spread with a heaping tablespoonful of the hydrogenated cottonseed oil. Two patients ate six such crackers on three different occasions, and one patient consumed nine crackers at one time. One patient was provided with a 1 pound can of the hydrogenated oil, which was used liberally as a substitute for butter. No ill effects were observed or reported from the ingestion of the oil in 3 younger patients. In the case of 2 older patients, aged 48 and 49, respectively, occasional severe attacks of asthma occurred during the

interval when they were taking the dispensed oil. These 2 patients have been victims of perennial asthma for more than twenty years. Especially critical examination of their responses to continued ingestion of cottonseed oil is, therefore, warranted. Our analysis of their histories is as follows: Asthmatic symptoms that were minimal for them were interrupted by exacerbation of symptoms at irregular intervals. Neither frequency, duration, nor severity of these attacks was influenced to any recognizable degree by continuance or cessation of the oil administration. It must be observed that the nature of the oil or the purpose of administering it was not revealed to the patients. They regarded it as medicine which might or might not benefit them.

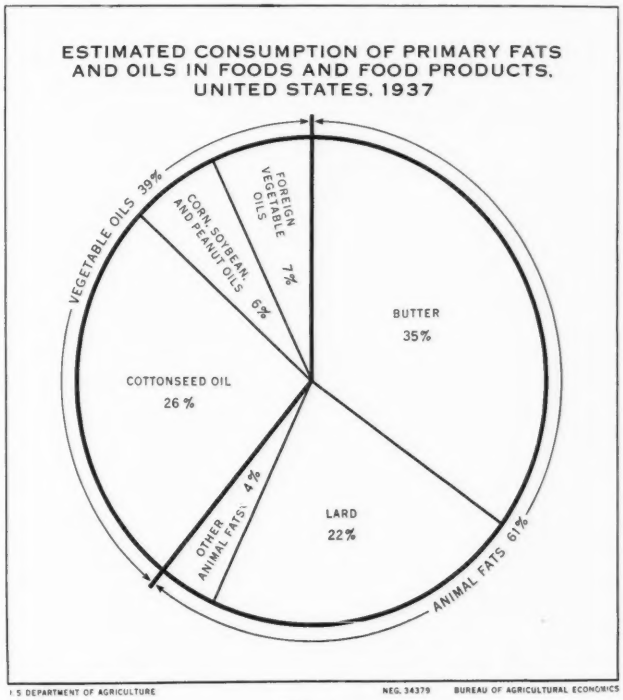
ESTIMATED CONSUMPTION OF PRIMARY FATS AND OILS IN FOODS AND FOOD PRODUCTS, UNITED STATES, 1937
VEGETABLE OILS 39%
FOREIGN VEGETABLE OILS 7%
CORN, SOYBEAN, AND PEANUT OILS 6%
BUTTER 35%
COTTONSEED OIL 26%
OTHER ANIMAL FATS 4%
LARD 22%
ANIMAL FATS 61%
U. S. DEPARTMENT OF AGRICULTURE
NEG. 34379
BUREAU OF AGRICULTURAL ECONOMICS

Fig. 1.

Finally, the refined cottonseed oil was administered orally to 8 individuals who had received a single sensitizing injection of cottonseed serum. Two sera from our type II patients were employed. Of each serum 0.1 ml. was used to sensitize a single skin site on the right upper arm of 4 recipients, thus making a total of eight sites available for reaction. Four days later 60 ml. of refined cottonseed oil, flavored with lemon juice, were given by mouth to each of the 8 recipients. No discernible or subjective symptoms of reaction in the sensitized sites resulted from ingestion of the oil. Three days later each recipient drank 30 ml. of an aqueous extract of the cottonseed kernel. Markedly

positive reactions developed within one-half hour on three sensitized skin areas; a mild reaction developed on one site at the end of an hour; itching, accompanied with a sensation of heat, was reported by 2 recipients. Two sites were clearly negative. Accordingly, six of the eight skin areas, sensitized by cottonseed serum, exhibited no detectable response following ingestion of cottonseed oil but reacted positively to the orally administered cottonseed allergen derived from the seed itself.

Our observations and conclusions may be briefly summarized. By every available test we have been unable to demonstrate a correlation between cutaneous and clinical sensitiveness to the specific allergen of cottonseed, and clinical sensitiveness to edible cottonseed oil or to hydrogenated cottonseed oil. The evidence we have assembled proves that the specific and exceedingly potent water-soluble allergens of the cottonseed embryo do not occur in refined cottonseed oil. Therefore, patients who are clinically sensitive only to water-soluble cottonseed extractives may safely be spared the inconvenience of attempting to avoid foods containing cottonseed oil.

Our findings are not submitted as evidence that clinical sensitiveness to refined cottonseed oil may not be encountered. The significance of this problem will be recognized in the implications carried by the statistics on consumption of primary edible fats and oils shown in Fig. 1.

TABLE I

FACTORY CONSUMPTION OF PRIMARY EDIBLE FATS AND OILS BY CLASSES OF PRODUCTS FOR 1936*

(Quantities in Thousands of Pounds)

KIND	COMPOUNDS AND VEGETABLE SHORTENINGS	OLEOMARGARINE	OTHER EDIBLE PRODUCTS
Cottonseed oil	918,866	108,106	178,330
Peanut oil	88,470	4,140	2,419
Coconut oil	38,427	150,465	60,020
Corn oil	430	1,238	51,017
Soybean oil	113,897	14,262	21,598
Olive oil, edible	------	------	3,972
Palm-kernel oil	627	2,400	12,490
Rapeseed oil	30,572	9	808
Palm oil	168,808	1,402	195
Sesame oil	33,120	57	16,728
Sunflower oil	208	5	920
Babassu oil	5,368	16,114	2,995
Other vegetable oils†	15,640	442	5,025
Lard	4,503	2,198	471
Edible animal stearin	36,358	3,550	4,370
Oleo oil	1,839	18,331	467
Tallow, edible	116,908	------	1,412
Fish oils	40,278	------	------

*From the U. S. Department of Commerce, Bureau of the Census, *Animal and Vegetable Fats and Oils*, 1937.

†Apricot, avocado, hemp, murumuru, mustard, ouricurry, raisin, shea, tea, tucum, walnut.

Cottonseed oil has long held a leading position in contributing to the supply of primary edible fats. For that reason, precise evaluation of the allergenic properties of refined cottonseed oil is important to the allergist. The fact should not be overlooked, however, that the fat in some particular food product may be from an oil-bearing seed which appears to be of relatively slight importance as a source of edible fat. These edible oils are in some measure interchangeable. Quantities of each kind consumed annually are determined by many factors. Hence the pattern of this picture of fat consumption changes continually. Table I lists oils that were unknown in the edible field five years ago. Some are increasing in importance; others will doubtless be absent from a like summary in the year 1940. All oils are subjected to essentially similar processing in preparing them for edible use. Therefore, demonstration of allergic sensitiveness to one kind of edible oil or fat will open a new field of investigation. Allergenic properties of the refined oil, according to our results, cannot be predicted by characterizing the allergens of the parent material. Moreover, we shall need to postulate the existence of allergens which differ significantly in composition from those now recognized among the nitrogenous water-soluble components of our foods. However, until further evidence concerning allergic sensitiveness to refined oils and fats becomes available, the conclusion seems justified that restrictions of these foods need not be demanded to assure the welfare of the allergic patient.

The authors wish to acknowledge the valued services of Dorris C. Chambers, M.S., for assistance in the clinical studies, and of Thomas H. Harris, B.S., for microanalytical determinations.

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DISCUSSION

DR. LEON UNGER, Chicago.—It is a privilege to be allowed to open the discussion on this splendid paper. The authors have shown that those who react to cottonseed protein can be divided into two groups. The first one is clinically not sensitive and gives negative tests to CS-1 and CS-1 picrate, the water-soluble protein-containing fractions which they have extracted from cottonseed.

Their second group is clinically and experimentally sensitive to cottonseed protein as shown by skin tests, by passive transfer, and by the occurrence of constitutional reactions.

Dr. Bernton and his co-workers have also demonstrated that patients who are sensitive to cottonseed protein are not affected by the ingestion of cottonseed oil, U.S.P., or hydrogenated cottonseed oil. This piece of work is in direct contrast to our previous belief. We have all been warned not to allow these patients to eat foods made with cottonseed oil. Thus, in one book there is the statement, "The oil of cottonseed contains active atopen and may, therefore, induce symptoms as an inhalant, ingestant, and contactant."

To show that this dictum is not true, Bernton and the others have fed U.S.P. cottonseed oil to patients who are strongly allergic to cottonseed protein. No symptoms have resulted. Furthermore, a water extract of cottonseed oil was tested in several ways and found harmless to these patients. Apparently inhalation tests by an atomizer were not tried.

I should like to add a little from my own experience and tests. Six patients who gave large reactions to ordinary cottonseed tests were selected, and all were strongly positive to the water-soluble protein-containing fractions CS-1 and CS-1 picrate which the authors were good enough to furnish me. Two of these patients also exhibited on passive transfer huge reactions to both ordinary cottonseed proteins and the purified derivatives. Cutaneous tests were sufficient at the transfer sites in these two cases. Passive transfer tests were not done in the other four patients.

In one youngster, there occurred, within 5 minutes after direct scratch tests, a rather severe constitutional reaction with asthma, rhinitis, and conjunctivitis. Prompt relief was obtained by an injection of epinephrine. This is the only patient in my experience who has developed a constitutional reaction after scratch tests. He was tested with ordinary cottonseed extracts and with the fractions.

Constitutional reactions do not occur, I believe, with the usual cottonseed extract when tested cutaneously. The derivatives CS-1 and CS-1 picrate must be tremendously potent. If they are to be used for hyposensitization, they must be diluted to at least 1:1,000,000,000 or more.

U.S.P. cottonseed oil was also supplied to me by the authors and was given to this highly sensitive boy and to two other patients in dosages beginning with one drop and increasing to one teaspoonful. No clinical symptoms followed. In addition, two patients had no trouble after eating cupcakes made from hydrogenated cottonseed oil.

Crisco was tried in 4 patients. In 2, no trouble ensued. In the child who had the constitutional reaction, gastrointestinal symptoms followed quickly on one attempt. Another trial with Crisco was followed by rhinitis. The fourth child wheezed a little after Crisco.

The authors have pointed out the complexity of the edible oil situation. I believe that all of us will now agree that cottonseed oil U.S.P. does not cause symptoms in cottonseed-sensitive patients. This is a real advance in our knowledge, but, clinically, it does not tell us as yet what we want to know. May our patients eat foods which are made with Crisco, Spry, Wesson oil, and similar products?

Two of my patients had trouble from Crisco; yet both of them took U.S.P. cottonseed oil without symptoms.

As the authors have stated, we cannot control the ingredients used by the manufacturers. Mixtures of edible oils may well be used. For example, the manufacturers of Spry refused to tell me which oil they use in their product. From other sources I am led to believe that they use cottonseed oil, corn oil, or cocoanut oil, and that they choose the particular oil by the market quotation at the time of manufacture. For all we know, they and others may mix edible oils in their products.

In the table shown I saw no reference to the use of oil from kapok seed. This oil is used very little for food. Because of the close relationship of kapok and cottonseed, a further study to include kapok oil would seem indicated.

For the present, we should encourage the use of U.S.P. cottonseed oil in these patients, but we should be very cautious in advising proprietary products which contain, among other ingredients, cottonseed oil.

Cottonseed also contains a toxic aromatic compound known as gossypol. This has been shown to be toxic when administered to some animals and is believed to cause symptoms in animals fed with cottonseed meal. I have conducted tests which prove beyond doubt that this substance, gossypol, does not cause allergic symptoms. I hope to be able to report these findings at a later date.

DR. BEN Z. RAPPAPORT, Chicago.—For the first time I have evidence that I am a very unusual fellow. While I am sensitive to cottonseed, I do not react like the patients discussed.

My sensitivity to cottonseed, apparently, is much greater than that of the cases discussed here. I do not want to go into personal details except to say that I am sure that all shortenings on the market—and this is not imagination—will give me abdominal discomfort at most times. While it is true that chemically one cannot detect the difference between cottonseed and many other oils, I know that I can. The appearance of canker sores, the edema of the lips, and occasionally hives, within a few minutes after its ingestion, has been witnessed by several members of the Chicago Allergy Society.

There must be something different about some cases that were not included in Dr. Bernton's study. I should like to have some of his cottonseed oil. I think that with some discomfort I could differentiate it from corn oil.

DR. ALBERT H. ROWE, Oakland, Calif.—This paper of Dr. Bernton's deserves our study and consideration because of the care with which it has been prepared. I must agree with Dr. Rappaport, however, that there are patients who are so sensitive to cottonseed allergens that clinical manifestations arise not only from the inclusion of small amounts of the commercial oils in their food but also from the intramuscular injection of cottonseed oil as a vehicle for hormones or drugs. Such patients may or may not give satisfactory scratch or intradermal cottonseed reactions.

I could cite several instances of such reactivity to cottonseed oil. One patient, especially, developed asthma within 3 or 4 hours after Crisco was included in biscuits which she had eaten, and again when Wesson oil was used in salad dressing. According to the author's suggestion, when the patient was entirely symptom-free, one teaspoonful of U.S.P. cottonseed oil was given with resultant asthma in 3 or 4 hours. We must remember, therefore, that such clinical sensitivity to allergens in cottonseed oil occurs in certain patients.

Since clinical sensitivity does occur, comment on the manufacturing technique of some companies is of interest. At times the apparatus is devoted to the manufacture of corn oil, at times to cottonseed oil, or to other oils. It is impossible to free the entire apparatus from all the formerly processed oil, and small amounts of one could easily contaminate a later manufactured oil.

DR. ROBERT L. BENSON, Portland, Ore.—Sensitiveness to the cottonseed can occur at a very early age. I have had an experience which is more unfortunate by far, as to general reaction, than Dr. Unger's. I think it is my duty to report here the death which I caused years ago.

A child 2 years of age had an allergic dermatitis, and through a

mistake—I know now why it occurred—the child died almost immediately after the administration of this antigen of cottonseed meal. I feel quite sure, as I said, that there was a mistake in the titer of it.

DR. UNGER.—Injected?

DR. BENSON.—Injected. The child had been previously scratch-tested, and through mistake, he died with symptoms that were very suggestive of allergic shock.

QUESTION.—What were you testing with?

DR. BENSON.—Cottonseed.

QUESTION.—What strength?

DR. BENSON.—I got the wrong strength.

DR. STEVENS.—I should like to recapitulate just a little to clarify some of the points on which there seems to be some confusion.

By fractionation studies we successfully isolated what we believe to be the principal allergenic fraction to which cottonseed-sensitive patients react. We then examined the refined edible cottonseed oil. I want to explain that we used U.S.P. cottonseed oil solely for the reason that this product is defined by the United States Pharmacopeia, and it is, therefore, one which is readily available to all of you. If you will use U.S.P. cottonseed oil, you will be using essentially the same oil that we used. I cannot say that for any other oil that I could refer to by brand name. U.S.P. cottonseed oil is representative of the refined edible oil of cottonseed, widely used in foods.

We have endeavored to determine whether the allergens of the seed were found in the cottonseed oil or in the hydrogenated oil. We used representative products of known history so that our results would be significant and applicable to the individual food products containing or made from refined cottonseed oil.

(Slide) I want to call your attention to the wide variety of oils that are used in food manufacture. Dr. Unger mentioned that kapok oil was not listed on this chart. That is true and that raises a point that I want to emphasize. Utilization of edible oils is a constantly changing picture. The following quotation from a recent report of the Bureau of Agriculture and Economics explains Dr. Unger's question:

"The 1936 Revenue Act placed a tax of 2 cents per pound on the seed (kapok seed) and 4½ cents a pound on the oil, in addition to a tariff rate of 20 per cent *ad valorem*, and no imports of the seed or oil were reported thereafter."

In this reference to edible kapok seed oil is an example of changes in quantities and kinds of oils and fats consumed, as the result of changes in tariffs, processing taxes, trade agreements, and so forth.

DR. BERNTON.—I must accuse Dr. Unger, perhaps, of a little bit of illogical reasoning, despite my great respect for him. He tells us one of his children reacted to Crisco. I do not know whether the Crisco was fed directly to the child or whether it was simply an ingredient of the food from which it was served. It was quite possible that the food was responsible.

Dr. Rappaport's experience is indeed at this present time unaccountable. I would want to know more of the facts about it. Of course, there is an exception to every rule, and Dr. Rappaport, we shall say, is exceptional.

INTRINSIC ASTHMA*

FRANCIS M. RACKEMANN, M.D.
BOSTON, MASS.

ALL is not allergy that wheezes.'' It is proper to recognize that allergy alone is inadequate to explain all cases of asthma, and it is time to encourage serious consideration of the possibility that either in connection with allergy, or quite independent of it, is some change in the physiology or chemistry of the organism which forms the fundamental basis for the asthma and the other symptoms that make up the asthma syndrome.

In the majority of cases, asthma depends upon a hypersensitiveness to foods or dusts. The peculiar reaction called ''allergy'' appears to be an adequate explanation of the symptoms which come and go accordingly as exposure to the offending substance is made or broken. The clinical history of patients with extrinsic asthma is usually clear. In the right place or at the right time of year, no symptoms occur, but in the wrong place or perhaps during the pollen season, asthma develops. The relationship between symptoms and exposure to the specific substance is direct and is usually demonstrable easily by the effect of hospital admission or of other changes in environment or diet. In most of these extrinsic cases, skin tests with the offending substances are positive. However, not all asthma can be explained in this way.

There is a considerable number of patients whose symptoms do not bear any relationship to environment. If the symptoms occur in attacks, it is impossible to demonstrate any change in environment, occupation, or diet which would explain them. Quite often the attacks start with colds, but in other cases, the relationship to colds is not so clear. It is this kind of asthma that is apt to increase in severity until at length the condition may become desperate and the patient is said to be in status asthmaticus. When such patients come to the hospital, they do not improve in a few days as do the extrinsic cases. Their asthma continues, evidently because whatever the cause, it is something which they carry with them into the hospital.

The diagnosis of intrinsic asthma depends not so much upon the exclusion of extrinsic factors as upon the history of attacks or of persistent trouble which bears no relationship whatever to outside factors. Furthermore, in most cases, skin tests when carefully made with proper technique so as to avoid irritation and the production of false positive reactions are persistently negative. The age of onset is later in the intrinsic cases.

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*From the Massachusetts General Hospital, Boston.
Read before the Annual Meeting of the American Society for the Study of Allergy, St. Louis, Mo., May 16, 1939.

In support of the idea that such a group exists is one important observation. In a series of about 2000 cases of asthma, which was extrinsic in origin and due to dusts and foods, not one patient has died of his asthma. An exception to this statement must be made to account for 2 or 3 patients whose death was purely accidental. Death has been known to follow a skin test made with too strong materials and by the intracutaneous method in a patient exquisitely sensitive, and it has occurred during or immediately after the injection of foreign therapeutic serum. In contrast, however, in a smaller group to be described presently of 283 patients with intrinsic asthma, there are so far 20 patients who have died, not only with asthma, but because of it, an incidence of about 8 per cent. This difference in mortality between the two groups is striking. What other characteristics are there to distinguish this difficult series of cases? Let us examine the clinical features of the group.

In a study of intrinsic asthma, it is possible to pick out certain groups of patients who can be distinguished by the fact that the beginnings and the clinical courses of their diseases have been quite different. The borderline patients, however, are far from clear, the groups overlap extensively, and it is quite impossible to be dogmatic concerning any subclassification of the series as a whole. However, certain clinical groups can be recognized and the list is presented in Table I, which gives figures for the number of patients in each group as well as other data. A discussion of these groups follows:

1. *Extrinsic Asthma Leads Directly Into Intrinsic Asthma.*—In a few cases, the isolated attacks that have gone on from year to year have usually, after the age of 40, become longer in duration and more frequent in occurrence. Secondary infections have changed a simple into a complicated process, so that eventually the asthma has become persistent and no longer varies with changes in season or environment. For example:

Dr. B. had ragweed hay fever for many years and was sensitive to horses, but in recent years, he was never exposed to animals. At the age of 48, an attack of bronchitis occurred toward the end of the ragweed season, and cough and wheeze persisted through that fall. After that time and each year thereafter, the fall has been a bad time for him. Later, bronchiectasis developed, and at the age of 60, his cough was worse and wheeze came with it off and on throughout the year. There was a gradual change from hay fever of a simple sort to bronchiectasis and later to asthma.

Another group is a little larger.

2. *Extrinsic at First, Then an Interval of Freedom With Intrinsic Asthma Coming Later.*

Dr. N. had ragweed hay fever since the age of 18, but in the early forties, this hay fever improved. The first asthma occurred at the age of 48, not after the hay fever, but in the month of January, so that he was confined to the hospital for three weeks,

After that, asthma was present constantly at all times of year, and in addition to the basic wheeze, he became subject to attacks of great severity, so that oxygen tents and other heroic measures became necessary. At the age of 62, he died in a violent attack of asthma. Autopsy showed extensive plugging of his bronchial tree with tough tenacious mucoid material. The heart was normal.

In patients of this group, the early incidence was asthma associated with hay fever, or sometimes with changes in environment. In each case there was an apparent spontaneous recovery before the onset of more trouble. During the interval which varied up to sixteen years, the patients were essentially well; then came asthma of a very different type. The new attack, which can be called intrinsic because it started without change in environment, diet, or occupation, came usually after a severe infection, often pneumonia, and then developed into persistent and constant trouble. The circumstances suggest that the new attack was in the nature of a conditioned reflex established by the early experiences and that the new infection served merely to reawaken the dormant condition. Such an idea, however, is really unnecessary because, as will be discussed presently, there is another group of patients in whom asthma begins suddenly in middle age.

Three of the patients in this extrinsic-intrinsic group have died. All 3 were men who had hay fever in their boyhood and then at the age of 31, 54, and 58, respectively, developed asthma rather suddenly. In each case, this asthma was of great severity which, once developed, continued persistently throughout the years, until the patients died in a relatively short time, namely, after 5, 5, and 4 years, respectively.

3. *Asthmatic Bronchitis.*—Asthmatic bronchitis is a term applied to those patients whose asthma is associated with upper respiratory tract infections. The disease comes in attacks, typically after head colds, and only two or three times a year, most frequently in spring and fall. These attacks are of short duration, with fairly long intervals between them. In about 30 per cent of the cases the onset was in childhood. In 50 per cent of the cases the onset was between the ages of 20 and 40, and in 20 per cent, it was after the age of 40. In many cases the same isolated attacks have continued off and on over a period of twenty, or even thirty, years, without any essential change. The group is a rather large one, comprising almost a quarter of the intrinsic patients. As might be expected, however, the problem is not serious. None of the patients observed so far in this group have died of their asthma, and relatively few of them have needed to be admitted to the hospital. Only about one-third of the group gave evidence of any trouble with their noses or throats, either in the past or present; and in none of the group was a true pansinusitis observed. Two of the patients had had polyps removed in the past, and one had polyps at the time of examination. About one-fifth of the patients had had previous operations on their

noses or throats—submucous resections, polypectomy, and excision of an antral cyst—but nothing more radical than these procedures, and it is important to note that in none of these patients did these previous operations afford any benefit so far as preventing further attacks or modifying the course was concerned. Skin tests were found to be positive in about a third of the patients, but in no one of them could the particular substance which reacted be identified as a possible cause of the attacks. These were positive tests that had no clinical symptoms to go with them.

4. *Persistent Asthma After a Series of Colds.*—Closely related to the group of asthmatic bronchitis, and of about the same size, is a group of patients in whom wheezy colds occur more frequently but still have periods of freedom between them, until at length, the intervals disappear, the asthma increases, and finally changes into the persistent, severe, often intractable type. One might observe that when the past history is of asthma that occurs in this way after colds, whether occurring only twice a year or more often, the chance of having the patient go on to severe persistent asthma is about 50 per cent. In this second group, lesions of the nose and sinuses occurred in over half the patients, a distinctly larger proportion. About two-thirds of the lesions consisted of pansinusitis and the other one-third of merely thickened membrane in the sinuses. Previous operations had been made on about half those patients who had lesions, most of them being a simple polypectomy; in addition four radical sinus exenterations had been made without benefit. Positive skin tests were observed in 13 of the 69 patients, but obviously had nothing to do with the cause of trouble. One man, skin sensitive to timothy and orchard grass, was always better and not worse in summer. Another patient, sensitive to horse, dog, and cat danders, lived in the city and was never exposed to animals. She could not remember that contact with animals had ever aggravated her trouble. A woman, sensitive to wheat, had never observed that wheat flour as dust in the kitchen increased her asthma, and when wheat as food was withdrawn from her diet, her symptoms were no better. Here then were more positive skin tests that had no symptoms to go with them.

Sudden Onset—Usually in Middle Age.—Those patients who develop asthma suddenly and for the first time in middle age, are particularly interesting. A plot of the ages at which extrinsic asthma of typical sort whether due to pollens, to animal danders, to feathers, or to house dust, first shows itself, consists of a curve that is highest in youth and then falls off rather rapidly until the proportion of patients who develop symptoms after age 40 becomes small. The mere fact that in the group to be discussed the age of onset is so late, is added evidence that extrinsic factors play little part. For convenience, the patients with sudden onset have been divided according to the apparent cause of that onset.

5. *Sudden Onset After Acute Respiratory Infections.*—More than 13 per cent of all the intrinsic patients had not had asthma before, or allergy for that matter, but developed it soon after an acute infectious process and then continued to have it persistently and severely from day to day, and without regard to changes in season or environment. This group contains only adults, about three-fourths of whom had their first symptoms after the age of 40. It includes twice as many men as women. Lesions of the nose and sinuses were found in 14 patients—in less than half of the total number; 11 out of the 14 had nasal polypi, and in 7 of these, a diagnosis of polypoid pansinusitis was made; the other 3 had thickened membrane of the sinuses. Operations were performed on 6 of the 14 patients—polyps being removed in three patients, and radical operations being made on the other three. One of these latter patients was free of asthma for about six weeks after the operation, and then the same old syndrome returned about as badly as before, but with occasional periods of improvement for several weeks at a time during which not more than two "shots" of adrenalin were needed to keep him comfortable. Sixteen months after operation, he died in a violent attack, and autopsy showed the typical picture of all bronchi obstructed by tenacious plugs.

6. *Sudden Onset—No Cause.*—In a similar group of patients about the same size, the asthma began suddenly, but this time without evident cause. So far as the patient could recall, the wheeze had begun insidiously without a preceding illness and without any change in residence, occupation, environment, or season. Like the preceding group, this one also was made up of adults, three-fourths of whom began their trouble after the age of 40. Men predominated over women, but not by a great number. Lesions in the nose and sinuses were found in two-thirds of the patients. Ten of them had had previous operations for nasal sinusitis and obviously without benefit to their asthma. Subsequently, follow-up showed that 3 of these patients died. It is interesting that 2 of these deaths occurred in those whose nose and sinuses were apparently clear of gross lesions. Positive skin tests were found in a third of the cases, but as in the foregoing group, the specific substance bore no relationship to the cause of trouble. The group as a whole is illustrated well by the following case.

Mrs. S., a tall, thin, married woman of 56 years, had a bad cold in March, but was well through the summer. In October she developed asthma rather suddenly and quite severely. She lingered on and after Christmas entered the hospital where she did well. X-rays and bronchoscopy yielded no significant findings, and she was discharged in four days. The asthma returned promptly and just as severely. In March of the next year she was admitted to another hospital, this time with no relief. Asthma continued for three weeks in spite of treatment with vaccines given every

three days, and large local reactions appeared (they may have become aggravated). When called to see her, I found emphysema with definite variations in the signs over certain parts of her chest (evidence of partial obstruction in one or other bronchus). The blood pressure was 170/110. Oxygen tents, Rowe's elimination diet, and glucose intravenously were all used with partial success, but she remained in the hospital three weeks longer. Through the spring and summer she improved slowly but steadily; gained weight from 93 to 105 pounds; and after September went seven weeks without adrenalin. Blood pressure fell to 124/100. During the next winter, she had occasional attacks. After eighteen months after onset, she was doing well.

The late age at onset, the continuation of asthma in the hospital and in spite of a very restricted diet, are against the diagnosis of allergy. Her skin tests were flatly negative. No lesions in her nasal sinuses have been found and her sinuses are clear. Her asthma was "intrinsic."

7. *Sudden Onset—Miscellaneous.*—In 2 patients the onset of severe asthma was attributed to a nose and throat operation; one, a woman of 55, with chronic sinus trouble, first began to have asthma after polyps were removed; the other was a man of 52 with frequent colds and chronic sinusitis, who dates his asthma from the time of a sinus operation. Both patients are still in trouble. Similarly, a woman of 43 first had asthma after tooth extraction. For sixteen months, her asthma continued in frequent attacks, and then after treatment with iodide and vaccines, she improved; in the last eighteen months she has had almost no trouble. Three patients attribute the onset to violent exertion, and all are still in some difficulties. In 7 patients asthma began at the time of emotional strain. Three of them are doing well; the others still have asthma. Asthma has long been considered to be of altered psychologic origin and it is patients of this type who tend to support the theory.

8. *Vasomotor Rhinitis, Then Sudden Asthma.*—Finally, the group which is of particular interest, comprises those who give a history of vasomotor rhinitis for several months before the onset of their asthma. Out of the total of 49 of these patients, 10 have died of asthma. Autopsies were obtained in 7 of them, and 5 showed bronchial plugs of typical character. In a sixth patient, the report describes "multiple areas of atelectasis"—due evidently to bronchial occlusion. The seventh patient had periarteritis nodosa. The group includes about 16 per cent of all intrinsic cases. Three-quarters of the group are women who began their nasal symptoms in their twenties and their asthma in their thirties. An important feature is that 75 per cent of these patients have had previous operations on their nose or sinuses, but who, nevertheless, still have sinus lesions. On the other hand, a few remain clear of sinusitis, and it is important that even in spite of this freedom, several have died. One cannot say that the nasal lesion is the reason for the fatal outcome. In 3 patients there was a story of bilateral radical antrum operations made several years ago and yet the asthma continues, in one case to death from asthma at the age of 49.

Skin tests in this group have been consistently negative, and many of the patients have been admitted to the hospital without change in their symptoms. The 31 patients who have had both previous nasal operations and present nasal lesions can be subdivided into three subgroups, comprising 7 girls, 8 middle-aged men, and 16 older women, respectively. The 7 girls are particularly interesting. Each of them suffered from chronic nasal discharge, frequent obstruction, and sneezing for many years, in 2 patients since early childhood. In each of them the asthma began suddenly between the ages of 22 and 29, except one who began at the age of 16. Of the 7 girls, 3 have died. The following story is typical.

Margaret S. developed attacks of "sinus trouble" at the age of 16. In the following year a left radical antrum operation was performed, and when her chronic nasal stuffiness persisted for another year, the antra were opened again, this time on both sides. The nasal discharge had been purulent at times. Wheezing began at the age of 18. Skin tests showed no reaction to any one of 80 different substances, including the common foods and dusts, and many of them were tested repeatedly. She was, however, sensitive to aspirin. White count was 10,000, with 1 per cent eosinophiles. Later, nasal polypi were removed on several occasions. Between the ages of 20 and 25, she was in hospitals nine times, once on the danger list after taking a tablet of aspirin. Many experiments with her diet were made.

In November, 1937, she (aged 26) was admitted to the Massachusetts General Hospital. She was given Rowe's elimination diet, oxygen tent, rectal ether, glucose intravenously, typhoid vaccine, and later aminophyllin intravenously, and finally bronchoscopy. After a long struggle lasting about three weeks, the daily number of doses of adrenalin was reduced from an average of 12 to 2, and finally to none. In January, 1938, she was transferred to the Psychiatric Service and was studied in the hospital carefully for six months, during which time her asthma flared from time to time. On July 1 she was discharged as improved, but two weeks later, she had another violent attack and died in twenty-four hours. Unfortunately, no autopsy was obtained.

The 8 men presented similar stories. The stuffy nose and frequent head colds began in the early twenties and led to asthma which continued persistently and increased steadily in its severity, despite all manner of treatment. Two of these men died.

F. X. S. was a young physician of 34, who developed a profuse watery nasal discharge with persistent obstruction, and then in two months developed asthma which continued intermittently for ten years until his death at the age of 44. He had had two attacks of bronchopneumonia, each followed by temporary improvement in his asthma, and he had had two extensive radical operations on his antra and ethmoidal sinuses, likewise with temporary improvement, but with no permanent gain. On several occasions, he had been admitted to the hospital when frequent doses of adrenalin were no longer able to control his asthma. He would vomit and fall into a virtual collapse. Twice, however, a sudden improvement in his asthma occurred without obvious cause, and the violent paroxysms ended by themselves as if by crisis. The last attack began like the others and progressed until he suffocated. Autopsy showed the lungs markedly distended, with the characteristic sticky plugs filling all of the bronchi. The precise findings will be described elsewhere.

The other man, S. T., a Jewish salesman, had been troubled with sinus symptoms for some months and then, following an operation on his antra, developed asthma suddenly and for the first time at the age of 30. From that time, asthma continued throughout all seasons and despite various admissions to the hospital for 13 years, until his death in a violent attack at the age of 43. He also was sensitive to aspirin. His treatment was always difficult and always unsatisfactory, despite the fact that every known remedy was tried. His sinuses were exenterated, local treatments to the nose were given, bronchoscopy was performed, his teeth were extracted, and finally, the thoracic chain of sympathetic ganglia was removed from his left side with the development of a typical Horner's syndrome but with no change in his symptoms. He died in the hospital where he had been for several weeks, the last attack beginning the same as many other attacks. Autopsy showed the classical picture of distended emphysematous lungs, the cut section of which showed tough, tenacious plugs that actually protruded above the cut surface.

TABLE I

INTRINSIC ASTHMA

Classified by Clinical History

	TOTAL CASES	MALES	AV. AGE OF ONSET	FAMILY HISTORY	SKIN TESTS	NASAL SINUSES			DEAD OF ASTHMA
						PREV. OP.	PRESENT LESIONS	BOTH	
1. Extrinsic into intrinsic	5	2	48	2	5	1	0	0	0
2. Extrinsic —OK— intrinsic	11	5	50	8	5	2	3	1	3
3. Asthmatic bronchitis	66	21	23	27	23	14	10	2	0
4. Series of colds	69	31	40	28	13	1	23	15	3
5. Sudden—acute infection	37	22	47	8	10	0	10	4	1
6. Sudden—no cause	33	18	49	13	9	1	11	9	3
7. Sudden—miscellaneous	13	5	53	6	3	0	4	2	0
8. V. M. R. into A.	49	11	37	21	10	3	4	31	10
Total	283	115	47	113	78	22	65	64	20

Previous Operations

$$\frac{22 + 64}{283} = 30\%$$

Present Lesions

$$\frac{65 + 64}{283} = 45\%$$

V.M.R. = vasomotor rhinitis.
A. = asthma.

The group of older women includes 8 who developed asthma in their thirties and 8 who started after forty. In the younger division, 2 died, both after an illness which was remarkable for its severity and its brevity. Two began asthma at age 36 and died at 38; the third began at 37 and died at 39. In each case there was a prolonged story of vasomotor rhinitis before the asthma. Two of the 3 women had had extensive operations and all 3 were found to have much nasal pathology at the time of examination. The second division includes one fatality.

Mrs. T. had had hay fever since the age of 20, with the development of nasal polypi that had been removed from time to time. At the age of 44 she developed

asthma of a severe type which became increasingly worse until her death at the age of 49. She died in the country where autopsy was not requested.

This group with asthma after vasomotor rhinitis is impressive if only because 10 of the 49 patients have died. Obviously, one thinks first of the relationship between the nose and throat and the asthma, but so far, such a relationship cannot be proved. Many sinus operations have been done without change in the symptoms, and even more important, several of the patients have become progressively worse in spite of the fact that the nose was clear.

DISCUSSION

The statement that asthma can depend upon an intrinsic cause can be based so far only upon the circumstantial evidence provided by the clinical history and the subsequent course of the disease.

In a paper presented recently before the Association of American Physicians, Dr. Greene and I[1] described a group of 8 patients, each of whom showed a striking clinical syndrome and were proved to have periarteritis nodosa. Four of the 8 patients died after an illness of only a few months, and we concluded: The syndrome of severe asthma with pain and numbness in the extremities and an eosinophilia of over 25 per cent points to the diagnosis of periarteritis nodosa and to a bad prognosis. In most of these cases there was in addition to the 3 typical signs, evidence of local hemorrhages with bleeding from bowel or lung or into the skin. Purpura was observed, and 2 of the 8 patients presented local nerve palsies due, no doubt, to small hemorrhages into the nerve trunks, so frequently described in the literature on periarteritis nodosa. Of especial interest was the fact that lesions of the pericardium and pleura with friction and fluid developed in each of our 4 fatal patients, but in none of the other 4 who are still living. Here at least is a group of patients having a form of asthma quite independent of extrinsic substances and due evidently to intrinsic causes.

In the preceding discussion I have tried to demonstrate that there are many cases in which the asthma continues regardless of many changes in environment or diet. Transfers to the hospital have no effect, and death occurs even though the patient is in the "allergically" perfect environment, an oxygen tent, or on an elimination diet. It seems inevitable that whatever the cause, it is something the patient carries with him. Whether the variations in the clinical histories, particularly the time and age variations as described above, indicate that there is more than one cause of the intrinsic group as a whole, is probably doubtful. The lack of any good basis on which to separate different groups of cases, the similarity of the symptoms at certain stages of the disease, and the fact that the end stage of chronic asthma is quite the same in all of them, are good evidences that the process underlying the

whole is a uniform disturbance. The attempt to subdivide the group according to the history is artificial and the figures must not be taken too seriously. It is very doubtful whether another group of the same size would show figures of the same magnitude for the different divisions. The relationship between this intrinsic process and any extrinsic factors is probably important, as will be discussed presently.

Meantime, there is one observation which appears to be a fact and is, therefore, important. In a study of nearly 2,000 patients of extrinsic asthma in whom the trouble was due to a dust or a food, no patient has died of asthma. However, in the literature there are one or two patients whose death was obviously accidental, since it was due to the injection of foreign protein, usually serum, as given for testing or therapeutic purposes. So far as I can recall, no death from asthma has occurred naturally from ordinary exposure to the offending substance.

In intrinsic asthma, on the other hand, the data presented above show that 20 deaths from asthma have occurred in 283 patients, a proportion of 8.2 per cent. The difference between the two groups is striking.

In Table II is a summary of certain data regarding the 20 deaths. The clinical groups in which they occurred are noted, and it should be emphasized that 10 of these deaths were in the so-called vasomotor rhinitis-asthma group. When chronic vasomotor rhinitis has persistent symptoms which are difficult to treat and when no adequate cause can be found for them by allergic or other methods, it seems that the prognosis for life itself may not be too good. Eosinophilia in the blood was high particularly in this vasomotor group. One of these cases was found to have periarteritis nodosa, and the fact confirms the impression that eosinophilia is a bad prognostic sign in asthma. What eosinophilia is, remains to be discovered.

Table II shows that sinus lesions were common in the fatal cases. Evidently, these lesions are part of the picture and are not a cause of it. However, 5 of the 20 patients have died even though the sinuses were clear. Autopsies obtained on 10 of the 20 patients showed in 8 of them the typical formation of tough sticky plugs which occluded the bronchi and caused death by suffocation. They were not described in Case 15 whose lungs contained multiple areas of collapse, no doubt because of complete bronchial occlusion. Case 20 with periarteritis did not have typical plug formation.

THEORIES

To explain intrinsic asthma, many theories have been mentioned in the past under various headings. "Bacterial asthma" was used in my first classification of 150 cases[2] published in 1918. Perhaps the designation still applies to the group now called "asthmatic bronchitis" in so

TABLE II

DEATHS FROM ASTHMA IN 1939 SERIES

PATIENT	AGES	CLINICAL CLASSIFICATION[b]	FAMILY HISTORY	SKIN TESTS	EOSIN.[c]	NASAL SINUSES			AUTOPSY
						PREVIOUS OPERATION[d]	PRESENT LESIONS	SUBSEQUENT OPERATION	
1. S. M.	15-34-36[a]	Extrinsic—OK—intrinsic	+	+	-	0	Clear	0	0
2. Dr. N.	18-58-62	Extrinsic—OK—intrinsic	+	+	4-16	0	Pansinusitis	0	Plugs
3. W. H. J.	18-54-59	Extrinsic—OK—intrinsic	+	+	0	0	Clear	0	0
4. Miss M. F.	47-51	After colds	-	0	-	0	Pansinusitis	0	0
5. Mr. W. T.	35-51	After colds	0	0	14	Polyp.	Pansinusitis	0	0
6. Miss N. C.	33-48-49	After colds	+	0	-	Rad. op.	Pansinusitis	0	0
7. R. P.	47-49	Acute U. R. I.	-	+	-	Antra wash	Pansinusitis	Bilat. rad. ant.	Plugs
8. R. L.	31-35	Sudden—no cause	+	0	9	0	Clear	0	0
9. Mrs. M.	49-52	Sudden—no cause	+	0	4-8	0	Thick	0	0
10. Dr. H.	59-61	Sudden—no cause	0	+	3	0	Clear	0	Plugs
11. Rev. P.	65-67-69	V. M. R.	+	+	-	Left ant. op.	Clear	0	Plugs
12. Mrs. H.	25-28	V. M. R.	+	0	1	Polyp.	Polyps	Rad. exent.[e]	Plugs
13. M. S.	16-18-27	V. M. R.	+	0	1	Double rad. ant.	Pansinusitis	Polyp.	0
14. Miss E. P.	25-38-38	V. M. R.	0	0	5-10	0	Thick	Antra opened	Plugs mucous
15. Mrs. I. R.	36-38	V. M. R.	+	0	8-11	Rad. op.	Pansinusitis	0	Multiple atelectasis
16. Mrs. W.	37-39	V. M. R.	0	+	8-12	0	Pansinusitis	Bilat. exent.	0
17. Mrs. T.	44-49	V. M. R.	+	0	8-13	Polyp.	Pansinusitis	0	0
18. F. X. S.	34-44	V. M. R.	+	0	1-16	0	Pansinusitis	Rad. exent.	Plugs; atel.
19. S. T.	38-43	A. after sinus op.	0	0	3-18	Rad. op.	Pansinusitis	0	Plugs
20. S. M.	36-38	V. M. R.	+	+	4-43	Sinuses drained	Pansinusitis	Rad. exent.	Fluid in pleura; periarteritis nodosa

[a]The first figure indicates the age at onset of the disease; second figure, age at death; and third figure, age of change in disease.
[b]Abbreviations in this column are: U.R.I., upper respiratory infection; V.M.R., vasomotor rhinitis; A., asthma.
[c]Percentage of eosinophiles in the blood, one or two determinations.
[d]Abbreviations are: Polyp., polypectomy; Rad. Op., radical operation on sinuses; Ant. Op., antrum operation; Rad. Ant., radical antrum.
[e]Radical exenteration.

far as many attacks do seem to be set off by head colds, or by other definite acute respiratory infections. Sometimes, the chest x-ray shows varying degrees of peribronchial fibrosis with prominent shadows at the hilus, and the question of some chronic bronchial or peribronchial infection arises. In a few patients who raise quantities of thick purulent sputum, such infections no doubt exist, but in other patients, the absence of infection is shown well by study of the lungs at autopsy. This study will be described later and at some length by Dr. Tracy B. Mallory, who now has examined a large series of patients. One thing he finds is that in many patients who died of asthma, emphysema is marked, and the bronchi are filled with an amorphous material, sometimes with a certain structure with strands simulating fibrin running across it. The bronchial glands are more prominent than normal and appear to be hypertrophied and overactive; hence comes the theory that the tough sticky exudate is merely a product of the excessive bronchial secretion. The important point to stress here, however, is that in the wall of the bronchi and around the outside, there is little or no evidence of an actual infectious process. In many, if not in most of our patients, therefore, the evidence of any true infection is small. The "vasomotor" cases, for example, have none of it that can be recognized. The process is probably not infectious.

"Reflex" asthma also has been used to indicate a direct nerve connection between the nose or sinuses and the bronchi. It is true that the relationship between lesions in the nose and asthma is close in some cases, but when a larger series of cases is studied, it becomes evident that many patients can die of asthma even when lesions of the nose are conspicuous by their absence. Reflex causes from the nose at least can account for only some of the cases.

The nutritional and the endocrine theories can be discussed together chiefly because so little is known about either of them, and yet as we look at recent discoveries in other diseases, it is fair to suggest that the true cause of asthma probably lies in one of these two categories.

The whole problem is complicated and, therefore, interesting. To explain allergy one must consider one unknown quantity—the capacity to develop sensitiveness which presumably is inherited. In the presence of the capacity, the precise kind and degree of sensitiveness, as well as the particular clinical manifestations, depend essentially upon exposure in occupation, environment, or season, plus probably certain other factors of minor importance, such as head colds or debilitated states, which explain why the patient has asthma rather than eczema; or better, why he develops hay fever from the grass pollens rather than from ragweed. Asthma can be explained in this way, provided allergy is present.

But what of the other cases where no allergy is demonstrable? To explain asthma of the intrinsic type, one must consider a second un-

known quantity—an x factor—which produces bronchospasm, which stimulates bronchial glands, and which causes edema in the nasal epithelium as well. Sinusitis and polyp formation are an important part of this picture, and my thesis is that, like the bronchial changes, they depend upon the same fundamental cause. Eosinophilia is a third result of the same process, and in the severe cases, one can add malaise; "allergic toxemia" it has been called.

To explain this symptom complex, one thinks first of histamine. Lewis[3] has shown that the reaction following irritation of the skin depends upon the release of a histamine-like substance from the skin cells. When histamine is injected into various animals, the symptoms that occur simulate closely those of anaphylactic shock. The theory then, that histamine or some substance like it might constitute a common denominator which arises from any sort of allergic reaction, is pertinent. Perhaps in asthma the body contains either an excess of histamine, or else it is deficient in the mechanism by which the normal amount of histamine is destroyed. However, one must not overlook the fact that even if histamine can be shown to be immediately responsible for the entire symptom complex, it will still be necessary to find out why and how this substance, normally present in the body, can suddenly begin to exert its harmful effects. By itself histamine is not the whole answer to the problem.

In recent months, Randolph[4] in our clinic, has tried to show that during the height of the asthmatic paroxysm, the amount of histamine in the blood was increased, but unfortunately, his results are essentially negative. If such a relationship exists, he cannot prove it. Whether this particular negative evidence is sufficient to rule out the question entirely is still doubtful, because in the blood itself histamine may be destroyed as fast as it is formed. Rose and Browne[5] have shown that, when histamine is injected into a rat, it disappears from the blood within a matter of seconds and is to be found chiefly in the kidneys. Perhaps in asthma histamine functions in the cells without appearing in the blood.

Meanwhile, histamine is not the only chemical effector substance capable of producing a so-called cholinergic effect. Acetylcholine likewise is shown to be released from cells as a result of nerve-muscle action. To study acetylcholine will be even more difficult, because the substance is so extremely labile. It breaks down rapidly because of the action of a natural ferment called choline esterase. Physostigmin (eserin) can offset this ferment, and in eserinized animals, the effect of injected acetylcholine is infinitely greater than in untreated animals. Physostigmin is a poison to asthmatics. More practical, however, is the relationship of acetylcholine to atropine. In animals atropine abolishes the effect of acetylcholine at once. In asthma atropine should relax smooth

muscles and inhibit glandular secretion, but in our patients, the effect of atropine is always disappointing, and the fact is strong argument against the theory that acetylcholine is concerned directly. How to account for the lack of effect from atropine is still another problem. Another cholinergic substance is adenosine, identified in the muscles by Drury and Szent-Györgyi.[6] So far nothing is known about adenosine in asthma.

Asthma may begin suddenly and the patient may pass from a state of comfortable breathing to one of severe dyspnea within a matter of seconds. Moreover, the paroxysm of asthma can sometimes end suddenly and quasi-permanently, as if by crisis. These sudden changes suggest that, if the cause is chemical, it is subject to prompt neutralization.

Adrenalin is always interesting. Does adrenalin neutralize the causative factor directly, or does it stop the symptoms merely by stimulating the sympathetic fibers, thereby producing a physiologic effect quite opposite to that of the parasympathetic vagus overactivity? When adrenalin is administered intravenously, diluted well in salt solution, the effect is often good; but in some cases, the effect is nil; and in extreme cases, as much as 3.0 c.c. of adrenalin has been added to a liter of salt solution and the whole run into the vein within a space of an hour. In this case the lack of effect is strong argument against the possibility that adrenalin has any direct neutralizing action. More reasonable is the theory that the drug failed to relieve because the sympathetic mechanism which it is supposed to stimulate had already been exhausted.

Disturbances of the acid-base balance and the concentration of electrolytes are suggested in other theories. At the present time, direct evidence in support of these theories is mostly lacking. At Beckman's[7] suggestion, moderate doses of hydrochloric acid and even of nitrohydrochloric acid have been given to patients with asthma but with effects that are not regular. How to explain the fact that acid seems to do well in a few cases remains unknown. Unfortunately, no careful studies of possible changes in the reaction of the blood have been made. Electrolytes present a similar problem, especially as the adrenal cortex is closely concerned with the metabolism of sodium. Potassium iodide is helpful to most asthmatics, and most authors think chiefly of the iodine ion and little of the potassium. Last year, however, Rusk and Kenamore[8] suggested that the effect of potassium iodide depended upon the potassium. Since then several of our patients with asthma have been placed on a "potassium regime" by which some of their daily sodium chloride intake was replaced by potassium chloride. Even though the results have been negative so far, the possibility will require further thought.

In the meantime the behavior of asthma in the presence of intercurrent diseases may throw a little light on the process. Mild infections, like colds, aggravate asthma, but severe infections with fever, like pneumonia; jaundice; heart disease with dropsy; surgical operations of almost any kind, especially if made under ether; trauma, as accidents; and starvation relieve it. In each one of these conditions, it is proper to think of a toxic product in the body which might destroy the asthmogenic substance. The effect points more to the surplus of something than to a deficiency of something else as the fundamental cause of the asthma syndrome. Beyond that it is hard to go at this present time.

SUMMARY

1. The term "intrinsic" applies to patients whose asthma bears no relationship to changes in season, environment, or diet. The group is not small. Some patients are free for several years between the early extrinsic and the later intrinsic asthma.

2. Deaths from asthma occur in 8 per cent of the intrinsic group, but in extrinsic asthma they are only accidental.

3. Some patients have asthma with colds two or three times a year. Later their attacks become longer and the intervals shorter, until the condition changes to one of persistent trouble.

4. There is a group of persons, mostly men, whose asthma begins suddenly in middle age and advances rapidly in its intensity, even to death. In half the cases, the onset occurs after an acute respiratory infection, but in the other half no obvious cause is apparent.

5. Finally, a most important group comprises patients, mostly women, whose asthma develops as a rather sudden complication of a chronic perennial vasomotor rhinitis. Of 49 patients, 10 have died, one with the lesions of periarteritis nodosa.

6. The theories concerning the nature of intrinsic asthma are discussed with the suggestion that allergy is only one of the exciting causes of a group of symptoms which together make a syndrome characterized by asthma, by lesions of the nasal and sinus membranes, and by eosinophilia, as well as by the less definite "allergic toxemia." Behind the syndrome must be some fundamental disturbance—an "x" factor—so far entirely unknown, but which may occur in excess rather than in deficiency. Even if it can be proved to be a histamine-like substance, the reason for its abnormal occurrence remains to be determined.

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(*See discussion on page 166.*)

ALLERGIC SYNDROMES IN THE ABSENCE OF ALLERGENS

PRESIDENTIAL ADDRESS

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THE title of these remarks may, according to common usage, be termed "Intrinsic Allergy." The substance, however, of this thesis fails to identify an allergen or the participation of any immunologic process.

The group of cases under discussion are difficult to identify at first glance, excepting perhaps by their relative intractability to treatment. Attention to their behavior, however, reveals characteristics which serve to identify them. They are comprised of patients with bronchial asthma, vasomotor rhinitis, and chronic urticaria, particularly. Those with asthma resemble the atopic type, in that there is no difference in the quality of symptoms or physical signs. The sputum is alike in each, as are the blood eosinophilia and prompt relief by epinephrine. There is usually an absence of a family or past history of allergy. Skin tests, if used, give no information. The onset is much later in life, as a rule during the third or fourth decade or later. Symptoms soon become severe and are intractable; emphysema develops remarkably quickly; and either recovery ensues with a tendency to relapse, or death occurs, sometimes within a few years after onset. Autopsy reveals the smaller bronchi to be plugged with thick, tenacious mucus. Of importance is the fact that antiallergic regimes, even when carried to the point of incarceration in a bare room with little or no food, have no beneficial effect. Moreover, it is noteworthy that many of these patients give no evidence of focal infection, endocrine disturbance, or other abnormality which can be identified as a possible cause of their symptoms.

Patients of this group with vasomotor rhinitis and chronic urticaria resemble those with asthma in their age of onset, negative results of allergic study, intractability of symptoms, and frequent absence of infection. The incidence of these cases compared with the atopic group is not established, but for asthma and vasomotor rhinitis it probably approximates 20 per cent or more of the total, whereas the great majority of patients with chronic urticaria, in contrast to the acute type, are probably nonallergic.

Since most cases of chronic urticaria present the characteristics of the nonallergic group, and particularly because the skin of such patients is so readily available for investigation, this disorder was chosen for study.

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Read before the Seventeenth Annual Meeting of The American Society for the Study of Allergy, St. Louis, May 16, 1939.

The circumscribed edema of an urticarial wheal is typically an atopic lesion. This fact is best expressed by a positive skin test. According to accepted theory, such a reaction occurs when the allergen (atopen) comes in contract with its specific antibody which is present in the skin. As a result, a histamine-like substance (H-substance) is released, and this in turn causes dilatation of the capillaries and permeability to their contained plasma which leaks into the surrounding tissue to form a wheal. A similar lesion can be produced by introducing histamine into the skin. The differences in infiltration of eosinophiles between the allergic wheal and infiltration from histamine is of no importance in this study.

The fact that an allergic wheal may be simulated by histamine, as well as by substances which provoke the elaboration of H-substance in the skin (pilocarpine, eserine), led to a further inquiry concerning the circumstances under which H-substance is formed in patients with chronic urticaria. The revelation by Lewis[1] and his associates that H-substance is released when the skin is injured by stroking, heating, freezing, galvanic stimulation, etc., was the groundwork on which further studies of histamine in the tissues were based. How H-substance is released is not yet clear, but Lewis' recent discovery of a new nervous system which seems to participate in the process is of much interest. He has shown that just as acetylcholine is released at the nerve endings when the cholinergic (parasympathetic) fibers are stimulated, and adrenin appears at the terminal filaments of the adrenergic (sympathetic) nerves when these are stimulated, so histamine or some similar substance appears when a newly discovered system of fibers present in the skin and mucous membranes of the upper respiratory tract are stimulated. To this new network Lewis has given the name "nocifensor nervous system." This is all too new to relate as yet to urticaria, but its significance in this connection may prove to be great.

Of very much importance to the present consideration are the observations of Grant, Pearson, and Comeau.[2] They investigated patients with so-called "physical allergy" in whom urticaria occurred on exposure to heat or after exercise. If a limb was plunged into warm water, a generalized eruption of wheals soon followed. These observers demonstrated that, if a tourniquet were placed around one arm sufficiently tight to occlude arterial flow and a leg were placed in warm water, the ensuing eruption would appear distal to the tourniquet. Obviously the only connecting pathway was through nerve impulses. This they demonstrated by blocking the external cutaneous nerve at the elbow and then again producing the eruption. Wheals occurred on the forearm only in areas not innervated by the external cutaneous nerve, whereas the anesthetized skin remained free. Further experimentation demonstrated that the pathway through which impulses reached the

skin below the tourniquet was the cholinergic (parasympathetic) portion of the vegetative nervous system. These nerves were shown in various ways to be involved in whealing in the patients under investigation.

On stimulation of cholinergic nerves, acetylcholine is released at their endings. It is evidently acetylcholine then that is responsible for the release of H-substance, and schematically the mechanism of whealing under the above circumstances may be expressed as follows:

Cholinergic nerve stimulation → acetylcholine →
H-substance → capillary permeability = wheal

Of much significance was the further observation that once acetylcholine releases H-substance, the process cannot be repeated for a period of some 36 to 48 hours. This is not due to a lack of acetylcholine but to an unresponsiveness of the mechanism as yet unexplained. This temporary refractoriness of the skin may be demonstrated in other ways. If, in a patient with urticaria, one outlines a group of wheals with ink, the succeeding crop will not enter the marked areas of the preceding crop for a period of 36 to 48 hours. The skin is evidently unresponsive to further H-substance. Or again, if pilocarpine, which stimulates cholinergic nerves, be driven into the skin by electrophoresis, a wheal promptly forms, evidently from the action of the released acetylcholine or H-substance. Once the wheal has disappeared, further whealing from pilocarpine at the same site will not occur for some 48 hours. That this is due to a failure of H-substance to form rather than a refractoriness of the capillaries themselves may be shown readily by the introduction of histamine at the same site; whealing occurs promptly.

This unresponsive phase is quite remarkable. It resembles in a way the antianaphylactic state following shock, and yet there is no indication that the phenomenon is an immune process. It would seem to explain why patients with so-called "physical allergy" from heat or cold are promptly relieved by daily baths at temperatures which at first cause urticaria. It may well explain the successful treatment of chronic urticaria with daily injections of histamine, about which so much is now appearing in the literature, since histamine presumably provokes the production of H-substance. We have successfully interrupted chronic urticaria in a group of patients by giving histamine intravenously, on the theory that H-substance would be released generally. The unresponsive phase was maintained by daily subcutaneous treatment.

So intimately is H-substance identified with whealing, one may suspect its involvement in the allergic-like edemas that occur elsewhere than in the skin. The fact that the newly discovered nocifensor nerves,

which appear to elaborate a histamine-like substance, occur in the upper respiratory tract as well as in the skin tempts the speculation that H-substance may be responsible for nonallergic vasomotor rhinitis. Moreover, since histamine perfused through isolated lungs causes spasm of the bronchial musculature, it would appear that essentially all the parts of the puzzle are present. Some of them are already fitted together, and it seems not too great an expectation that with the intensive studies of H-substance now being conducted in England and in this country, a completed picture may be revealed before long.

I trust that the purpose of these remarks will be understood as I have attempted to convey them. They imply that the group of cases under discussion lack essential criteria to identify them with the immune processes of atopic disorders which they exactly simulate clinically. Moreover, not even in its broader meaning can the word "allergy" safely be applied to them. The possibility that the underlying mechanism involves the release of H-substance is considerable, whereas the factors that cause this mechanism to operate in this group of cases are quite unknown. As allergists, we should be prepared to broaden our viewpoint.

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DISCUSSION ON "ALLERGIC SYNDROMES IN THE ABSENCE OF ALLERGENS," BY DR. HARRY L. ALEXANDER; AND "INTRINSIC ASTHMA," BY DR. FRANCIS M. RACKEMANN*

DR. CHARLES H. EYERMANN, St. Louis.—It is a deferential custom not to discuss the president's paper, so that I would add to Dr. Rackemann's remarks my personal admiration for a lucid and succinct presentation. It required twenty minutes for Dr. Alexander to give us only an outline of one of the factors which operate in cases of intrinsic asthma, so that any discussion of Dr. Rackemann's very fine presentation will, of necessity, be a bit sketchy.

The concept of allergy has emphasized the wheeze so that, in the clinical conditions discussed by Dr. Rackemann, one is tormented by the fact that clinical hypersensitivity exists when some of the usual criteria of allergy are missing, particularly positive skin tests, and one is bewildered by the number of stimuli which seem to induce the wheeze. I know but few other clinical situations wherein one must be the exemplar of the allergo-internist.

I believe that the subdivisions of intrinsic asthma, mentioned by Dr. Rackemann, can be classified into two broad groups. First there are patients who have inspiratory and expiratory wheezing, more or less constantly, without total incapacity, with nonpurulent sputum and the tendency to spontaneous remissions. It is in this group that one fears to have missed a clinical sensitivity.

*See page 147 for article by Dr. Rackemann.

In the second group, there is also more or less constant wheezing with exacerbations characterized by voluntary re-enforcement of the expiratory muscles, and this terminates with abundant purulent sputum, to be followed by a variable relatively asymptomatic period. Here, infection appears to be the dominant cause. Dr. Vaughan has felicitously phrased allergy as "the great intruder," and so it appears to be in the occasional case in all of Dr. Rackemann's clinical subdivisions. It is in this latter group that it intrudes rather frequently.

Dr. Rackemann conjectured about factors which may influence or even produce the immunologic mechanism. I should like to add two of my own. In 1927 I studied a girl, 17 years of age, who had angio-edema. The edema came and went as she either ate or abstained from chocolate, mustard, pork, and beans. The skin tests were negative. Eighteen months ago this patient, now a married woman with three children, developed vasomotor rhinitis while avoiding the foods which produce angio-edema. The vasomotor rhinitis is dependent upon ingestion of beef, and the skin tests still are negative. I believe it reasonable to infer that in this instance the same immunologic mechanism induces the vasomotor rhinitis and the angio-edema. Is it not possible then that the immunologic response in skin negative cases of bronchial asthma may be similar to that in angio-edema?

May it not be also possible that the immunologic response is a matter of synergistic action—a response similar to the flare-up of quiescent sites of intracutaneous or other forms of cutaneous testing by the administration at a distant site of the same or even an unrelated allergen, or similar to the apparent synergism existing in some cases between inhalants and ingestants? These hypotheses, added to what we already have, are more confusing than clarifying, but as long as clinicians have enough curiosity to try new therapies which will stimulate laboratory experimenters to disprove them, I believe we need not despair the eventual solution.

I believe that the wheeze is more likely due to obstruction by secretion than by bronchospasm; whatever the process which produces the inspissated, amorphous, tough, sticky material that plugs bronchi at post mortem is also present in the nose, for I have observed this same rubbery material extracted during life from the ethmoid sinuses in two patients, and through an operative antral window in another.

I would also remark that influenza bacilli have been so frequently the dominant organism in the patients who eventually have died of asthma that I am beginning to believe the presence of influenza bacilli indicates an unfavorable prognosis.

I am in agreement that death is unlikely through the absorption of allergen in usual amount through the usual channel; however, I have witnessed one death in an adult resulting from ingestion. I have also been the medical advisor of chronic asthmatics who needed adrenalin frequently and who were found dead in bed. It is not an unusual mode of exitus in my experience.

I am confident that with clinical studies such as we have heard this morning, with laboratory experiments such as Dr. Alexander told us about, the percentage of those who wheeze of unknown etiology will decrease.

DR. WARREN T. VAUGHAN, Richmond.—We have recently become so impressed with the importance and significance of bronchial plugs that at the present time we feel that every resistant asthmatic should be given

the benefit of a diagnostic bronchoscopy. In some we find no bronchial plugs nor any great accumulation of thick, tenacious mucus, and it seems to me that they would be the type of cases in which we should proceed with Dr. Alexander's suggested plan of therapy.

Dr. Milton B. Cohen, Cleveland.—I think we should not pass by the importance of the presentation which Dr. Alexander gave us in relation to some of these problems. I do think that a good deal of our difficulty is due to the fact that we think about asthma and hay fever or vasomotor rhinitis instead of thinking about the whole widespread disease. It manifests itself in every way.

These studies, therefore, are extremely important because they help us reclassify and ultimately may help us put certain things together so we will understand them.

The histology is very interesting. The histology of the wheals described by Dr. Alexander is identical with that of the wheals one produces when he puts ragweed in the skin; the histology of the lungs in asthma is the same, and that of acute anaphylaxis is the same. If the animal lives thirty or forty minutes, you will see thickening of the septa and of the mucous membranes and fibrinous and mucoid material in the bronchi quite like you see in the patient who dies in the attack.

If histologically these are the same, why have we not the same right to follow the histology when we see it as we do when we see a tumor metastasizing in various organs? I think we have, and I think this conception of Dr. Alexander has shown us that the H-substance produced, whether an immunologic hive or a nonimmunologic hive, is the cause of the hive or the reaction. Certainly we could consider that many of these reactions which we cannot explain may be due to nonimmunologic methods producing a substance giving us symptoms and pathology identical with those produced by immunologic methods.

Dr. Armand Cohen, Louisville.—In trying to explain the effect of histamine, I think we should bear in mind the excellent work of Best, recently reported in *The Journal of Physiology*.

He calls attention to the fact that histamine can be produced, not only by crushing or bruising of tissue, but likewise from a bacterial action reducing histidine to histamine. Likewise, he found that certain tissues, particularly in the lungs, liver, heart, and intestines, were able to neutralize the effect of histamine. This was found due to an enzymelike action. This enzyme he called histaminase.

I want to call attention to this work of Best because it does offer us a chemical explanation of the effect of histamine in addition to the neurologic and biologic explanation offered this morning.

Dr. George L. Waldbott, Detroit.—Dr. Rackemann anticipated that we might not all agree with his classification of intrinsic and extrinsic asthma. I wonder how we could possibly make such a differentiation if we realize that practically all of our patients with asthma are multiply sensitive and if we also realize that one of the main criteria upon which such a differentiation can be based is the skin test which in so many instances cannot be relied upon.

Take, for instance, the cases of asthma associated with menstruation. This group of cases could well be termed "intrinsic asthma." Yet practically all of these patients develop asthmatic attacks from extrinsic

sources. The same is true of the patient with a sinus infection. While his infection may be the dominating feature, there are always any number of extrinsic causes which bring on attacks.

I am glad that Dr. Vaughan brought up the question of bronchoscopy, which I would rather call therapeutic than diagnostic bronchoscopy. I feel certain that this measure was lifesaving in a number of my patients who were in a dying state.

DR. OSCAR SWINEFORD, JR., University, Va.—I shall limit my discussion to a few aspects of the papers which seem to me to require comment. One is that a considerable number of Dr. Rackemann's patients were in the old-age group. I think it possible that a significant number of those people had cardiac asthma and that they should have been digitalized as a therapeutic test.

The quotation "All that wheezes is not allergy" should remind us that carcinoma of the bronchi, tuberculous and postpertussis hilum glands in children, aspirated foreign bodies, congenital and other causes of bronchial stenosis are associated with the phenomenon of wheezing, not necessarily restricted to the area in which the lesion is present.

We must remember, too, the well-recognized secondary and the more questionable primary roles of physical agents, emotions, and the vasomotor instability of the menopause in the phenomenon of wheezing.

DR. RACKEMANN.—I appreciate the discussion, and I am sorry there is not time for more of it because I am delighted that you do not all agree with this idea.

Now, as I see this thing broadly, it is like this: I believe that up to now we have all been working on the second story of this house. This morning Dr. Alexander has brought us down as far as the first story, but we still have to go to the basement and the foundation; in other words, whereas many of the symptoms may be produced by histamine, we have still before us the question of how is it that histamine can exert its action. Is there an excess of histamine in the blood? Is there some difference in the normal mechanism by which histamine is destroyed?

All I can offer is the suggestion, the possibility, of some unknown substance which will have the following properties: It will be responsible for the stimulation of bronchial glands and the outpouring of mucus, which is asthma. It will be responsible for the thickening and hypertrophy of the nasal sinus membranes, which are so common. It will be concerned, of course, with eosinophilia. It will possibly be concerned with vascular lesions which have been described. Finally, it will be concerned with the malaise and generally diffuse symptoms which these patients have and which we term "allergic toxemia."

My message (and I am sure Dr. Alexander's message) is to encourage you to think of this whole system of diseases as possibly dependent upon a real disturbance of physiology or chemistry which is very fundamental and which awaits much further investigation.

CRITICAL REVIEW:

IMMUNOLOGICALLY ALTERED SKIN REACTIVITY IN NONATOPIC PERSONS

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I. INTRODUCTION

A CERTAIN relatively small group of people ("atopic," "allergic") have untoward symptoms from repeated exposure to what, for want of a better name, has been called "foreign protein." This is regarded as an abnormal phenomenon. If this is abnormal, it necessarily follows that there is a much larger group who do not have symptoms from such exposure.

In any attempt to understand the atopic person, a study of the normal person's reactive processes to stimuli which do harm to the atopic is of the utmost importance. So much attention has been paid to the abnormal that too little has been paid to the normal.

In this review I have tried to synthesize data from many isolated investigations, have drawn some conclusions which seem well warranted, and have suggested others for consideration, which are not so clear and, whether correct or incorrect, are certainly debatable.

II. THE INCIDENCE OF POSITIVE SKIN TESTS IN UNSELECTED NONATOPIC PERSONS

Baker,[1] 1920, scratch method; 937 tests with foods in 25-75 children; 10 positive reactions, 4 of these to salmon.

Peshkin and Rost,[2] 1922, scratch method; 502 children tested with foods and environmentals; 10 per cent doubtful reactions.

Moro,[3] 1932, scratch method; 326 infants tested with egg white; all negative.

Rackemann and Simon,[4] 1936, intracutaneous method; 60 adults tested with ragweed, horse serum, kapok, cat hair, feathers; 50 per cent positive to one or more; kapok positive in 22.

Grow and Herman,[5] 1936, intracutaneous method; 150 adults tested with egg, milk, feathers, horse dander; 55 per cent gave one or more positive reactions. (Rather strong extracts used.)

Pearson,[6] 1937, intracutaneous method; varying number of adults tested with different allergens such as horse dander, horse serum, chicken feathers, wheat, egg white; about 33⅓ per cent gave one or more positive tests.

I have been unable to find any data for scratch tests in normal adults.

Conclusions.—Despite the probable inclusion of some atopic persons in all these series and the variations in technique and interpretation, it seems fair to conclude that positive scratch tests are not common in normal children or infants, but that positive intracutaneous tests are common in unselected adults who have no atopic symptoms. What their significance is, is another question.

It is also evident that the degree of skin hypersensitivity is by no means as great as it is in atopic persons.

III. THE PRODUCTION OF ALTERED SKIN REACTIVITY IN NORMAL PERSONS BY ARTIFICIAL INJECTION*

Hooker,[7] 1924, 27 per cent positive after diphtheria toxin-antitoxin.

Tuft,[8] 1932, 27 per cent positive after diphtheria toxin-antitoxin.

Simon and Rackemann,[9] 1934, atopic and nonatopic persons, mostly nonatopic. Injected 0.1 c.c. guinea pig serum, diluted 1:10, 1:100, and 1:1,000, intracutaneously, once a week. One gathers from their paper that *all* gave positive tests, usually after the third or fourth injection, if the stronger dilutions were used. Reagins were occasionally present if the degree of skin sensitivity was high. Atopics reacted no differently from nonatopics.

Mote and Jones,[10] 1936, injected 69 normal persons repeatedly with small amounts of rabbit serum. Skin hypersensitivity produced in 82 per cent. Reagins were often present, but only twice after eight months. They mention especially that there is a great difference in the ease with which different persons become sensitized.

Davis,[11] 1938, tested 100 persons who had received a previous therapeutic injection of horse serum; 88 per cent positive.

Conclusions are obvious.

Comment.—It is significant to note that in all these investigations, the sensitizing antigen was one with which there had been no previous contact. Neither Simon† nor Sulzberger† could reproduce these results with egg white. It is also significant to note that the degree of skin hypersensitivity was, as a rule, not high. No mention is made of scratch tests, but it seems certain that many of these persons would have failed to react by this method.

IV. THE PRODUCTION OF SKIN HYPERSENSITIVITY BY NATURAL CONTACT IN NORMAL PERSONS

Anderson and Schloss,[12] 1923, added cow's milk, egg white, sheep serum, and almond to the diets of nurslings who had never eaten these foods before. Positive skin tests (intracutaneous) and precipitins ap-

*I have not included Brunner's work (J. ALLERGY 5: 257, 1934) because it was done with atopic persons. He was able to sensitize only rarely with injections of common allergens. Would his results have been different if he had used antigen to which there had never been a previous exposure?

†Personal communication.

peared in 50 per cent in about ten days. They lasted only a short time. Moro later found the same thing for milk and, in addition, that no transferable antibodies were present.

Schloss, Lippard, and Johnson,[13] 1936, studied 229 infants, children, and adults. Every one was consuming about a quart of milk a day. Complement fixing antibodies were present in practically all infants between the ages of 1 and 15 months, only occasionally present between the second and fifth years, and never found in persons over 5 years of age.

They considered three possibilities to account for the loss of antibody and skin test with increasing age: (1) that the gastrointestinal tract becomes impermeable after a while; (2) that complete digestion takes place; (3) that some unknown immune reaction neutralizes foreign protein even if it is absorbed.

Comment.—It seems likely that all of these factors may be operative, but that they vary with different proteins. Schloss himself showed that milk protein did not often reach the blood stream after infancy. The infant is in a special situation as regards milk, which is not paralleled by any other food with adults. He is taking enormous quantities of it in relation to his weight; it was not intended by nature that he should take such a high protein diet as is furnished by cow's milk, and his digestive function is not adapted to it. The situation is quite different for some other proteins. Wilson and Walzer[14] found that egg, fish and nuts penetrate into the blood stream in the majority of persons of all ages. Mitchell and Hamilton[15] speak of the "coefficient of digestibility" of proteins which has been worked out by the biochemists for many food proteins. Egg white has the lowest of all; under the best conditions only about 85 per cent is digested. There is, therefore, a great variability in the ease with which different proteins are absorbed unsplit. Egg white goes through my own intestinal mucosa very easily after eating only a small amount, and wheat and milk, not at all. I have no positive skin test to egg, although I probably did for a while as an infant. What is my present immunologic status? I am not sensitized to egg white, nor can I be sensitized to it. Am I *immune* to it? At all events, I have learned how to deal with it in such a way, or have become tolerant, or acclimatized to it, so that it is inert, although it is a foreign protein in my blood stream.

Conclusions.—The evidence suggests that, for foods which are regularly eaten, there is normally a gradual adjustment or immunization to any unchanged protein which is absorbed, and that during the first part of this process there may be a phase of skin hypersensitivity which is afterward lost. There is also some suggestive evidence to indicate that it may not be possible to sensitize a normal person to a food, provided he has been eating it regularly for a considerable period of time.

ENVIRONMENTAL ALLERGENS

Colmes, Guild, and Rackemann,[16] 1935, studied 32 bakers and got positive intracutaneous reactions to various grains in 47 per cent. Only one had symptoms. "To become skin hypersensitive is a common property of mankind, while the capacity to express the sensitivity clinically is the property of those in whom the intrinsic factor, the activator, is in operation."

Likewise, Schick[17] has said, "Everyone may be made allergic, but very few become so hyperergic that they are asthma or hay fever patients."

Salm, Jahlin, and Dunufeldt,[18] 1936, made intracutaneous tests on bakers, cavalrymen, and persons in several other specialized occupations; 38 per cent of the bakers gave positive tests to rye, and 23 per cent of the cavalrymen to horse dander.

"In any particular calling, the allergens that were constantly exerting their influence gave positive tests in a relatively high percentage, and only in those. Clinical symptoms were rare."

Comment.—How does one account for the fact that so many normal persons, with apparently adequate exposure, do not develop positive tests? I do not see how this question can be answered from the facts, without undue speculation, until more data are available. The issue is beclouded by the fact that one does not know for certain, as regards this group with negative tests, that any antigenic protein has actually entered the blood streams, and exposure by natural contact can by no means be compared to accurate and controlled exposure by injection.

The fact that there is great variability in the reactive mechanism of different persons, even when antigen is injected, might be used as an argument for the thesis that the only strictly normal persons are those who do not develop positive skin tests. If this is so, then those who do show skin hypersensitivity, but who have no symptoms, must be either put into the atopic group or a special group must be made for them midway between the atopic and the normal persons. Such a conception does not seem the most reasonable one, and as far as I know, provided there is no atopic family history, there is no evidence to indicate that such people are any more likely to develop atopic symptoms than if they had no positive skin tests.

The fact that so many develop altered skin reactivity when injected with definite amounts of protein at definite intervals is strong evidence that such a result is a normal phenomenon; and that an identical result would take place if the same amounts of antigen entered the blood stream, no matter by what route, despite the fact that it occurs in perhaps only a third or a half of those who are exposed by natural contact.

If the word "antibody" or "reagin" is discarded for a moment, it may be said simply that, as a result of stimulation of the immune

mechanism with antigens of the type concerned in the present discussion, the serum may acquire, among other possible changes, a property that it did not have before: that of fixing a new quality in certain tissue cells, so that on subsequent contact with the antigen, they show altered reactivity.

The fact that the normal person often develops positive skin tests leads one to believe that this tissue fixing property, although more characteristic of the atopic person, has been developed likewise in the normal person's serum to a certain extent, whether or not altered reactivity can be produced in the skin of a second person by transfer of the serum.

Conclusions.—The normal person, with the exception of developing symptoms, seems to be able to do immunologically everything that the atopic person can do, only he does not react so intensely or for so long, and he needs greater stimulus before he reacts at all.

V. THE OCCURRENCE OF POSITIVE SKIN TESTS IN NONATOPIC PERSONS IN RELATION TO AGE

With continually eaten foods the normal person apparently tends to react for a short time in early life after the food is first eaten, and then the reactivity is likely to die out. For other substances, the age relationship is somewhat different, and for this we shall consider not atopy alone, but allergy in its broader sense, according to Pirquet's original definition.*

Smith[19] and Tuft[20] quote the following results with tuberculin:

AGE	PER CENT POSITIVE
0- 6 mo.	0.7
6-12 mo.	3.1
2- 3 yr.	7.4
6- 7 yr.	16.0
12-13 yr.	45.0
Adults	90.0

Hill[21] tested 60 eczematous infants and children with trichophytin and obtained two doubtfully positive reactions.

Hill[21] tested 60 normal infants and children with oïdiomycin and obtained three doubtfully positive and two definitely positive reactions.

Adults react to both of these antigens so frequently that a positive test is of no diagnostic value.

Hill[22] tested 20 normal infants under 1 year of age with house dust (intracutaneous). No positive reactions.

*"The vaccinated individual reacts differently to the lymph, the luetic to the syphilitic virus, the tuberculous to tuberculin, and the one injected with serum reacts differently to the serum, than does an individual who has never yet come into contact with the given agent. He is, nevertheless, as yet far from being immune, because of this. All we can say about him is that his capacity to react has been altered. I suggest the word "allergy" to designate this general concept of altered reactivity." (München med. Wchnschr. **30**: 1457, 1906.)

Hill[23] tested 38 normal adults, with 39 per cent positive reactions to the same dust extract.

Hill[23] found that 46 mothers of eczematous infants gave 63 per cent positive reactions to the same extract. As a rule, the reactions were larger than in the other group of adults.

Hill[22] tested 20 normal infants under 1 year of age with goose feathers. No positive reactions.

Grow and Herman[24] tested 150 normal adults with goose feathers (intracutaneous) and obtained 16 per cent positive reactions.

Straus[25] tested 119 newborn infants with *Rhus toxicodendron*. All negative.

Most adults react.

Comment.—The Frei test for lymphogranuloma inguinale, the mallein test, and the skin test for undulant fever, trichinosis, and certain types of streptococci are all illustrations of a fundamental law which is becoming continually more important in clinical medicine: that, after stimulation with a wide variety of antigens, the altered reactivity of the organism as a whole is paralleled by altered reactivity of the skin, and that such altered skin reactivity, being a usual phenomenon, is not abnormal. True, the antigens concerned in the allergy of infectious disease work in a somewhat different way from those concerned in atopy, but the broad underlying principle is the same—altered reactivity after exposure. The attacking agents responsible for the infectious diseases possess the power of unlimited reproduction and have toxins within themselves, or can elaborate them, which directly poison the host. Leave out these two properties, and the antigens of the "allergic diseases" can be more closely compared with these agents, obeying much the same fundamental laws. There is no reason to believe that powdered streptococcus or *Bacillus abortus* dust would not produce allergic rhinitis or asthma with positive skin tests, as well as any other nonliving environmental allergen.

As Dr. Dienes said in New York, at a dinner of the Allergy Society in 1937, much profit is to be gained by comparing the immunologic phenomena produced in the "allergic diseases" with allergy and immunity in the infectious diseases. After all, these phenomena, although differing in several ways, are produced by basically the same event, attack of the organism by material which is unnatural and repugnant to it, and have basically the same end result, altered reactivity.

We do not say that the almost universally positive tuberculin and oïdiomycin tests in adults are nonspecific. What should be said of the positive reactions in normal persons to various antigens commonly associated with atopy?

While all would agree that irritative nonspecific reactions occur if too strong extracts or too much test fluid is used, the evidence presented in this review suggests to the writer that a considerable proportion

of the positive skin reactions obtained in nonatopic adults are specific immunologic reactions and are not abnormal, that the adult has lived long enough to have been marked by his environment, in contrast to the infant who has not. If all forms of immunologically altered reactivity, atopic or nonatopic, are included under the term "allergy," as most allergists believe they should be, then the only truly nonallergic person is a very young person.

It would not be possible to find a single person in a group of 100 adults who would fail to react to one or more of the following: house dust, feathers, tuberculin, trichophytin, *Rhus toxicodendron*. There is a vast distinction, however, between being allergic and being a sufferer from an allergic disease; practically everyone who has lived for any length of time is allergic; very few are so constituted that they have an allergic disease. It seems that any person, from birth onward, is likely to go through immune reactions to a variety of antigens; that there is a stage in this immunization, if the stimulus has been strong enough, in which altered skin reactivity may be a normal part of the picture; and that this phase may vary a great deal in its intensity and duration, depending on many factors, both intrinsic and extrinsic. It further seems that in the atopic person, this phase, when produced by certain organic, but nonliving, antigens because of an innate peculiarity in the person, is intensified and prolonged, and tolerance, or immunity, if it is permissible to call it so, is reached with great difficulty, if at all.

QUESTIONS

1. Should positive intracutaneous skin tests in normal persons, when proper technique has been used, be considered specific immunologic reactions?

2. Are these reactions part of a normal immunologic process?

3. What is the status of a normal adult whose blood stream is being continually penetrated by egg white, who had a positive skin test to egg and antibodies for a while after he first began to eat it, who has a negative skin test to egg now, and who is apparently nonreactive to egg in any way? Should he be called immune to egg in the same sense that he is immune to measles?

4. Is it proper to take the concept that the normal person tends toward tolerance or immunity in his relations with "foreign protein," but that it may be normal for him to go through a phase of hypersensitivity before he attains this tolerance, and that the hypersensitivity is of the same sort that the atopic person has, but of much less degree?

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Annual Review

ALLERGY AS RELATED TO RHINOLOGY AND OPHTHALMOLOGY

LITERATURE FOR 1939

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A REVIEW of the literature on the subject of allergy from the standpoint of ophthalmology and rhinology for the year of 1939 shows a comparatively small number of presentations devoted to this subject. In general, there appears to be an increasing interest in the part played by allergy in paranasal sinal disease. There are, however, far too many articles on the subject in which allergy is given no consideration whatsoever. On the other hand, in those instances in which allergy is considered, there are definite indications that often allergic management has not been adequate. There is great need for better cooperation between the allergist and the otolaryngologist. Only by this cooperation can certain important factors be determined. For example, further statistical studies should be made on the incidence of allergy among nasal and sinal cases in general and on the incidence of polypoid or hyperplastic changes in nasal allergy, hay fever, and asthma. The frequency of reversible, as compared with irreversible, changes in these cases should also be determined. The comparative incidence of acute and especially chronic infections and more definite indications for surgical interference remain yet to be estimated.

BIOCHEMISTRY

Mittermaier[1] reports further observations on the chemical aspects of nasal polyposis. He found that the protein content of the polyp fluid ranged between 0.5 per cent and 1.0 per cent, while the protein content of normal serum is about 7 per cent. This indicates that the polyp is not formed by the stasis of fluid. On the other hand, Mittermaier is of the opinion that it is probably caused by a greater permeability of the blood vessels. He suggests the following simple test to determine the allergic response in cases of polyposis. Two-tenths of a cubic centimeter of physiologic saline solution is injected intracutaneously. A small wheal is formed, followed by a secondary wheal. The secondary wheal disappears in about six to twelve minutes. In patients with hyperplastic states who show a tendency to edema and polyposis, he found that usually the secondary wheal does not occur, and the primary wheal disappears in a much shorter time than six minutes. It is concluded that per-

sons who show a rapid resorption of saline solution have a tendency toward polyposis, probably due to a certain degree of retention of salt in the skin. In treatment, he suggests a salt-free diet leaning toward the alkaline side of the acid-base ratio and a careful avoidance of any tendency to acidosis.

Chavanne[2] concludes that clinical observations reported in the literature coincide with the results of his experiments as to the relations of the nasal secretion and endocrine glands. Castration is followed by atrophy of the glands of the nasal mucosa and lowering of the functions of secretion of the mucosa. Pathologic conditions of the nasal mucosa resulting from diminished or increased function of the genital organs, as well as transient disorders of the nasal mucosa in the course of menstruation and pregnancy, are reported. The anterior lobe of the hypophysis and the thyroid inhibit the nasal secretions. The same result is obtained by administration of extracts of the anterior lobe and the thyroid. Thyroidectomy increases nasal secretion. Thyroid extracts act through their effects on the thyroids. Extracts of the anterior lobe of the hypophysis act by controlling several endocrinotropic substances which are concerned with the nasal secretion.

The occurrence of satisfactory results sometimes noted in allergy patients following the administration of one or more endocrine gland extracts suggests that these glands must play a part in the allergic mechanism.

ANAPHYLAXIS

Harlowe[3] reports a case of procaine idiosyncrasy in which, following the injection of 0.5 per cent solution, the patient complained of faintness, severe headache, dyspnea, and nausea. The patient became cyanotic, vomited, and developed a rapid and weak pulse, and then general clonic spasms began. The operation was not performed, but nine days later another physician injected a 1 per cent solution of procaine with epinephrine, and the patient expired on the operating table.

ALLERGY OF THE NOSE AND PARANASAL SINUSES: DIAGNOSIS AND TREATMENT

In a review of 3,657 consecutive cases seen in eye, ear, nose, and throat practice, Kuhn[4] noted that 720, or 20 per cent, had nasal complaints. An analysis of this group of 720 cases showed that 140, or 19.4 per cent, had nasal allergy. This group of cases of nasal allergy constituted 3.7 per cent of the total reviewed.

The cytology of the nasal secretions was determined in 88 of the 140 cases of nasal allergy. In 26 cases an eosinophilia of over 50 per cent was found. In 34, it varied from 10 to 50 per cent. In 28 cases there was an eosinophilia of 1 to 10 per cent. In 52 cases no smears were

made. The skin tests showed the following positive reactions: inhalants, 57 (40.7 per cent); foods and contacts, 7 (5 per cent); and inhalants, foods, and contacts, 76 (54.3 per cent).

The results of treatment were as follows: satisfactory by allergic management only (avoidance and desensitization), 67 (47 per cent); satisfactory by allergic management plus local treatment, 38 (27 per cent); satisfactory by allergic management plus surgical treatment, 30 (21.7 per cent); failures, 5 (3.5 per cent).

A consideration of Kuhn's statistics shows that only 19.4 per cent of the nasal cases had allergy. Our percentage of nasal allergy has been between 40 and 50 per cent of all nasal cases.

In a discussion of the conservative management of the sinuses, Jervey[5] considers briefly the most important phases of this problem. His statistics on the incidence of sinusitis and allergy are interesting. During the years 1924 to 1928, 421 cases of sinusitis and 11 cases of allergy were noted among 1,566 ear, nose, and throat cases. From 1929 to 1933 there were 328 cases of sinusitis and 20 cases of allergy among 1,395 patients. From 1934 to 1938 there were 305 cases of sinusitis and 76 cases of allergy among 2,419 patients. Jervey states that the number of diagnoses of sinusitis is gradually falling. Diagnoses of allergy and other conditions (nutritional disturbances and traumatic rhinitis) are increasing. It is noteworthy that the percentage of allergic cases increased from 0.7 per cent during the first five-year period to 3.1 per cent during the last five-year period. According to our statistics, the incidence of allergy among ear, nose, and throat cases is about 16 per cent. The incidence of allergy in any individual private practice is proportional to the accuracy of the diagnosis.

In his discussion of allergic rhinitis Jones[6] states that it is difficult to differentiate clearly perennial hay fever and allergic rhinitis. Those cases in which the primary symptoms were sneezing and rhinorrhea and in which the nasal mucosa was pale were considered as perennial hay fever. The cases with a red nasal mucosa were considered as allergic rhinitis. Is there a justification for making this distinction between a pale and a red mucosa? Considering all cases of allergy in the nose as nasal allergy, there is a definite variation in the type of mucosa observed, namely, normal, slightly pale, markedly pale or edematous, or red. Nasal polyps are usually present with the pale mucosa. There appears to be no reason, therefore, for the introduction of additional terminology.

In a study of the relationship of nasal allergy and other manifestations, Agar and Cazort[7] conclude by emphasizing the following points: (1) studies of the nasal and bronchial secretions give the only reliable means of diagnosing infected and infectious asthma; (2) a submucous resection properly done is of great benefit in a large percentage of cases

of hay fever and asthma; (3) in sinal disease, conservative surgery is preferable and offers good results in inverse ratio to the duration and severity of the asthma.

Patterson[8] discusses his experiences with the external operation of the ethmoidal labyrinth which he advocates in cases of polyposis. He states that by this method the nose may be permanently freed from polyps. Although almost 100 per cent of the cases of nasal polyposis are of allergic origin, no reference is made to this factor.

In discussing the subject of sinal disease in general, Fletcher[9] enumerates such complaints as sneezing, profuse discharge, and nasal obstruction, among other symptoms such as headache, pain, and fever. He further states that the formation of polyps is the result of long-continued infection. He also remarks that infection from the sinuses may spread to the tonsils and adenoids. He defines acute sinal infection as simply a "cold in the head" and chronic sinus disease as "catarrh." An infection is mentioned as the usual cause of disease. Allergy is not considered as an etiological factor in these cases.

In a general consideration of the subject of allergy in otolaryngology and its relation to other manifestations, Hansel[10] discusses the various allergic lesions which may affect the eye, ear, nose, and throat, and their relation to manifestations of allergy elsewhere in the body. In nasal and sinal diagnoses a special emphasis is placed on the careful consideration of the following factors: (1) nasal and sinal symptoms; (2) the gross pattern changes; (3) the cytology of the secretions; (4) x-rays; (5) histopathologic findings; (6) bacteriologic findings. In those cases with marked pathologic changes, attention is called to the importance of determining whether complicating infections are acute, subacute, or chronic.

In a further consideration of allergy in otolaryngology and its relation to other manifestations, Hansel[11] discusses problems in diagnosis and treatment and illustrates some important points by case reports. From the otolaryngologic standpoint, a great deal of stress is placed upon the necessity of complete studies of the nose and paranasal sinuses without which atypical cases may be easily overlooked. It is emphasized that radical surgical procedures should be deferred until allergic methods of treatment have been instituted, for satisfactory relief of symptoms and the control of pathologic changes are dependent upon adequate allergic management.

The following reports on the end results of various types of surgical interference on sinal disease by Hempstead,[12] Faulkner,[13] Salinger,[14] and Arbuckle[15] were presented as a symposium before the American Laryngological, Rhinological, and Otological Society in Chicago on May 10, 1939. In general, they represent a free discussion of both conservative and radical procedures. It is noteworthy that allergy was considered an

important factor in the cause of sinal disease, and it was given more attention than in previous symposia of a similar nature. In general, however, it is evident that more attention should be directed to greater accuracy in diagnosis, utilizing particularly the information obtained from cytologic and bacteriologic studies. There is much need for closer cooperation between the otolaryngologist and the allergist.

A great deal of emphasis should be placed upon the prophylaxis of sinal disease. Acute infections should be properly managed so that the chronic process may not develop. The use of chemotherapy no doubt will play a great part in obtaining better control of the acute and subacute infections. The early recognition and control of the allergic processes should lower the incidence of the development of hyperplastic and polypoid changes with secondary infection. The incidence of hyperplastic and polypoid changes in patients with nasal and sinal allergy is between 20 and 30 per cent, depending upon the type of cases under consideration, the highest incidence occurring in patients with perennial nasal allergy, hay fever, and asthma. These are the patients who represent the largest percentage of the group which is subjected to surgical interference.

With proper allergic management in the early stages of the disease, it is evident that the incidence of marked pathologic changes could be very materially reduced, and consequently, the number of patients requiring some type of surgical operation.

Among otolaryngologists there exists a great deal of difference of opinion as to the type of operation (radical or conservative) most effective in the treatment of both infective and allergic involvement of the maxillary sinus. Hempstead emphasizes the importance of preoperative studies including the use of the antroscope. By this means the presence of polyps, cysts, and tumors, as well as the condition of the lining mucosa, often can be determined.

Hempstead's observations were based upon a study of 385 patients treated by the conservative type of intranasal operation. It is noteworthy that, in 22.5 per cent of the cases, the infection was caused by dental caries. It is noteworthy that polyps were not found in cases of infection of dental origin. Among the 385 patients treated by the conservative method, it was necessary to perform the Caldwell-Luc operation upon only two of them. In both cases the antrum was filled with polyps. Hempstead refers to the report of Tucker who, in 1928, reported that, in a series of 673 patients with chronic maxillary sinusitis, the intranasal operation was performed with success in all but six in whom the radical type of operation was necessary. It is noteworthy that, in the nine patients in whom polyps could be seen at operation, the polyps could not be observed later.

Hempstead further states that, when infection complicates an allergic process, a dry antrum cannot be obtained until the allergic condition has been controlled. For postoperative treatment dry suction is recommended instead of irrigations with aqueous solutions.

It was finally concluded that the intranasal window operation has many advantages, the most important of which are: reaction is much less severe than with the radical operation; there is a minimum of injury to the lining mucosa; polypoid and badly infected mucosae have been seen to return to normal after the establishment of drainage and ventilation. It is significant that among 1,634 cases collected from the literature by Hempstead, a good result was obtained in 97 per cent of the cases treated by the establishment of an intranasal antrum window.

In evaluating the end results of intranasal operations on the ethmoid, frontal, and sphenoid sinuses, Faulkner emphasizes that a satisfactory outcome is usually dependent upon the performance of a complete operation. Although many of the cases of hyperplastic and polypoid disease require surgical interference, allergy has not as yet been given due consideration as the most important part of the treatment. The general belief has prevailed that failure in these cases is usually the result of poor or incomplete surgical operations. While this is certainly true in the treatment of the pure cases of suppurative sinusitis, it is not necessarily true in the allergic cases. Often the conservative removal of nasal polyps and hyperplastic tissue is all that is necessary in most cases in which adequate allergic management has been instituted.

In discussing the subject of end results of external operations on the maxillary sinus, Salinger states that conclusions as to the effectiveness of this operation must be based on the relation of the local findings to the symptoms, a consideration of the patient as a whole, and a determination of the degree of care and skill with which previous conservative treatment has been applied. He advises the Caldwell-Luc operation only when there exists within the antrum a degree of pathologic change which is beyond the hope of repair by any means short of complete removal and when the pathologic change so diagnosed is the cause of the symptoms for which the patient seeks relief. The pathologic changes to which reference has just been made are divided into two groups—the one associated with various degrees of local symptoms of which the patient is aware, and the second more or less silent or occult but associated with manifestations of disorders elsewhere in the body. The first group, according to Salinger, is usually characterized by the symptoms of nasal discharge, obstruction to breathing, headaches, and frequent colds. The patient may have been treated by various minor procedures, such as antral lavage, tamponade, removal of polyps, and other intranasal operations, and the process has manifested cycles of comparative relief between attacks, according to the weather and the patient's general health.

Salinger further points out that examination during an attack reveals a purulent or mucopurulent discharge, with or without polyps, thickened red lateral pharyngeal bands, cloudiness of the antra, usually more marked on one side, and marked obscurity of the shadow on a roentgenogram. Between attacks the symptoms vary from comparative normalcy within the nasal passages to the presence of mucopurulent discharge, polyps, and a red or glazed pharynx. A persistent cloudiness of the antrum by x-ray and transillumination is considered a constant finding. Even though irrigation yields little or no secretion, with the above roentgenologic findings, Salinger feels that the conclusion that the lining membrane of the sinus is not normal is inescapable. Salinger gives the greatest consideration to the appearance of a thickened, irregular membrane at a time when the patient has the fewest subjective symptoms and a minimum of objective findings. In other words, he states, if the sinus looks bad when the patient feels best, there can be no doubt that a chronic unresolved process is present which will yield to nothing less than radical extirpation. Salinger concludes by stating that he has never been disappointed in the operation when the preoperative diagnosis was based on sound facts and careful study and when possible allergic factors had been thoroughly investigated and taken care of.

From the standpoint of clinical symptoms, course, and physical findings, it is evident that in cases of this type we are dealing mostly with allergy. In every instance it is important in the beginning to determine whether the process is a pure infection, an allergy, or an allergy complicated by an acute, subacute, or chronic infection. There should be no difficulty in making this distinction if the clinical history, physical findings, and roentgenologic findings are correlated with the cytologic and bacteriologic findings. The cytologic determination alone is of indispensable value in making an accurate diagnosis. Without it, no one can be 100 per cent accurate in diagnosis, especially in determining the presence of acute, subacute, or chronic complicating infection. As Salinger points out, the roentgenologic findings are most significant during a period of quiescence of symptoms. The persistence of a cloudy antrum at this time does not, in my opinion, however, justify a radical operation in every instance. If the process is allergic and there is no significant infection as determined by cytologic and bacteriologic examinations, operation may not be indicated unless there has been no improvement with adequate allergic management. In any event, satisfactory end results of surgical interference of all types on allergic disease of the sinuses are more dependent upon adequate allergic management than upon properly performed operations. Allergic control of symptoms and pathologic changes may eliminate the necessity of surgical interference entirely or may so ameliorate the process that conservative procedures are adequate and radical interference is not indicated.

In his discussion of the end results of external operations on the frontal, ethmoid, and sphenoid sinuses, Arbuckle states, "Rhinologists have seen the rise of popularity of surgical treatment of sinal disease on the basis that infection was the underlying cause in all cases. During all this time, in a certain number of cases, relief was not obtained by such treatment. Then they found that many such conditions are not of infectious origin but are allergic. Accordingly the popularity of operative treatment has decreased almost to the exclusion of certain types of surgical intervention in favor of antiallergic treatment and, occasionally, endocrine treatment."

Arbuckle further calls attention to the rapidly increasing general belief that allergy is a most important factor in the cause of the complaint in well over half of all persons suffering with symptoms of sinal disturbance and that, when the condition is correctly diagnosed and properly treated, operation is contraindicated except in instances of infection of a type for the relief of which surgical intervention is indicated. Therefore, it is emphasized that the necessity of differential diagnosis between infections, sinusitis, and allergic sinusitis is obvious. Arbuckle also emphasized the importance of cytologic examination of secretions in all cases and the necessity of instituting adequate allergic study and care.

In Arbuckle's experience he has noted that, as a rule, when allergic sinuses are operated upon, symptoms disappear for from six weeks to six months, after which the allergic symptoms recur when the patient is exposed to allergens to which he is sensitive. This is in agreement with other observers. He also remarks that he has observed a number of patients with nasal polyps in the early stage of development in whom the polyps disappeared with allergic management and remained absent until their growth was restimulated by an acute infection or an allergic exacerbation. On the other hand attention is called to the fact that polypoid tissue which has become fibrotic does not disappear with such treatment.

ALLERGY AND SINUSITIS IN CHILDREN

Nasal polyposis is almost exclusively a disease of adult life, except the choanal form, which not infrequently occurs in children. Laff[16] reports an unusual case of deforming and recurring polyps in an asthmatic child. He also reviews the literature on this subject but finds comparatively few reports.

The case reported by Laff was that of a male child, aged 15 years, who had had nasal symptoms and asthma since the age of 7. The polyps were first removed at the age of 9 years. When the patient was 15 years old, Laff removed the polyps again and performed a bilateral ethmoidectomy.

Nasal polyps in children are extremely rare before the age of puberty. On several occasions we have noted edematous thickening of the lower

edge of the middle turbinate and in the middle meatus in children under the age of 10 years, but we have not observed a case of definite nasal polyps before puberty. We have, however, noted several instances of polyps in children at the ages of from 13 to 16 years.

Barnett and Carnahan[17] emphasize that allergy is a common cause of rhinitis in children, whether acute or chronic, seasonal or perennial, recurrent or constant, and that it is often unrecognized. A great deal of importance is placed upon the value of cytologic examinations of nasal secretions in diagnosis. Allergic control is vital if necessary associated surgical procedures are to be of benefit. Barnett and Carnahan point out that removal of infected tonsils and adenoids may aggravate symptoms in a child with uncontrolled allergy.

Mitchell[18] submits a report of his experiences in the management of sinusitis in children extending over a period of twenty years. Among a group of 145 patients, 74 have been observed up until the present time. An additional twenty-six were kept under observation for five years, and eighteen were followed for three years. All these patients had chronic sinusitis.

Mitchell emphasizes the importance of the consideration of allergy in the diagnosis and treatment of sinal disease in children. He states that many of his failures were due to the fact that he did not recognize and properly treat a complicating allergic condition.

The role that surgery of the paranasal sinuses plays in the asthmatic child was investigated by Creasy[19] in a group of sixty children between the ages of 5 and 14 years. In five patients there was slight veiling or edematous changes shown in the x-ray plates. Eight of the cases showed membranous antritis. In twenty-one there were combined antritis and ethmoiditis. Of these twenty-one patients, seven had antritis and ethmoiditis on the left side, and in fourteen the same process was on the right side. Five patients showed bilateral ethmoiditis with involvement of one antrum. Seven had bilateral antritis, six had bilateral antritis and ethmoiditis, and two had pansinusitis. It is significant that in this group of sixty cases there were three males to each female. The results were reported as follows: Fifteen patients were asymptomatic after two years; thirty-three were asymptomatic for from one to three months. In three patients the nonbeneficial results were attributed to poor cooperation, and in six the degree of improvement was not stated. Among the complications of the surgical procedures, one patient had bilateral mastoiditis, one had scarlet fever with postscarlet mastoiditis, one patient had pyelitis, and four had acute otitis media requiring myringotomy.

Creasy does not state the total number of persons from which these patients were selected. The incidence of pathologic changes reported, therefore, is unknown. Cytologic studies of secretion apparently were not made; at least, it was not stated that this laboratory procedure was

utilized in diagnosis or in determining the presence of infection. The diagnosis of sinal infection in asthma cases certainly cannot be based upon the x-ray plates without the correlation of cytologic examinations. It is significant that an undue number of complications followed the instituted surgical procedures.

Crooks[20] presents his observations on a series of 100 cases of sinusitis in children. In twenty-four patients the tonsils and adenoids were removed because of the presence of mucopus in the antra. Further observations of these patients showed that after six months sixteen still had the sinal condition. The following symptoms were most commonly listed: nasal or postnasal discharge in 84 cases; frequent colds in 83; cough in 82; mouth breathing in 62; headache in 44; and otitis media in 44. Diagnosis was made by transillumination, roentgenograms, and direct puncture. The predominating bacteria recovered from the sinuses were pneumococci and streptococci. When the antrum did not clear up after six irrigations, Crooks did an intranasal antrotomy. Of the 100 patients, 52 were cured, 32 improved, and 16 unchanged.

The majority of the papers which appear in the literature on sinal disease in children are of this type, in which allergy is not considered as an etiological factor. Even if an attempt were made to exclude cases of this type, it could not be done accurately without cytologic studies of the nasal and sinal secretions. It is probable that the group of cases reported by Crooks consisted of both allergic and infectious or combined types.

Birdsall[21] reports his observations on a series of cases of nasal sinusitis in children occurring over a period of two years at the Paddington Green Children's Hospital in London. The ages of the patients ranged from 2 to 13 years: thirty-six were boys, and forty-four were girls. Sixty of the eighty patients were between the ages of 5 and 9 years, inclusive.

Birdsall states that the symptoms were found to occur in the following incidence: nasal obstruction, 39; cough, 33; frequent colds, 32; rhinorrhea, 21; pain, 14; throat symptoms, 12; anorexia, 8; otorrhea, 7; bronchitis, 6; listlessness, 5; postnasal discharge, 4; asthma, 4; and epistaxis, 3.

The tonsils and adenoids had previously been removed in nineteen or one-half of the patients with nasal obstruction. In thirty-five of these thirty-nine cases, nasal obstruction was associated with rhinorrhea. Cough was an outstanding symptom in thirty-three cases. Twenty-seven patients had nasal discharge. In the remaining six cases cough was attributed to bronchitis. Two had asthma. Of the thirty-two patients with frequent colds, three had bronchitis. Of the remaining twenty-nine, fourteen had previously had a tonsillectomy. Twenty-one patients had definite rhinorrhea.

In discussing etiology, Birdsall states that, in children, sinusitis is insidious in its onset. Only one case of acute sinusitis was oberved among the eighty cases. The duration of symptoms varied from one week to nine years, the average being two and one-half years. In thirteen instances some specific illness preceded the onset of symptoms. In seven of these the sinusitis followed whooping cough. It is noteworthy that thirty-three of the children in this series had undergone tonsillectomy without benefit. The average period following tonsillectomy and preceding observation was three years, during which the symptoms had gradually been increasing in severity.

Mucopus was found in the noses in forty-two patients. In thirty-six of these the prominent symptoms were cough, frequent colds, or rhinorrhea. Fourteen showed opacity of one or both antra upon roentgenographic examination. In eleven, mucopus was found upon antrum lavage.

Thirty-four patients showed significant changes in the nasal mucosa, such as pallor, redness, or pseudoatrophy. Birdsall states that in chronic infection the mucosa becomes pale and edematous. Mucopus was noted in the nasopharynx in twenty-seven cases. Enlarged tonsils were noted in twelve patients. In two they were removed. In ten the condition of the tonsils improved with treatment of the sinuses. Five patients had a dermatitis of the lip and anterior nares.

In thirty-seven cases an x-ray examination of the sinuses showed changes in the antra in thirty-five instances. In twenty-two patients the ethmoids were also involved. Bilateral involvement of the antra was noted in twenty-four cases.

The results of treatment were as follows: Of the eighty patients, fifty-nine received adequate treatment. Fifty-two of the fifty-nine patients were cured, thirty-four after a course of displacement therapy with ½ per cent ephedrine solution in 1 per cent saline, thirteen after combined treatment by displacement and antrum lavage. Five were subjected to antrotomy, and four were improved.

This report has been reviewed in detail in order to offer some constructive criticism of the diagnosis and treatment of sinusitis in children. In the management of nasal and sinal diseases in children accurate diagnosis cannot be established and adequate treatment instituted unless allergy is considered as an etiological factor. Sinal disease in children must be considered as purely allergic, infectious, or a combination of allergy and acute, subacute, or chronic infection. In our experience 95 per cent of the chronic sinal diseases in children are primarily of allergic origin. The differentiation of the above types of sinus disease can be readily accomplished by correlating the clinical history and the physical and x-ray examinations with the cytology and bacteriology of the nasal and sinal secretions. Accurate differentiation usually can be made on the basis of the cytologic examination alone, a pure eosinophilia denoting

an uncomplicated allergic process, and a neutrophilia or a combination of an eosinophilia and a neutrophilia signifying various degrees and types of complicating infection.

A survey of the clinical history and physical and x-ray findings in Birdsall's group of cases suggests a very high incidence of allergic disease. No cytologic or bacteriologic studies were reported. It is, therefore, impossible to determine the exact incidence of allergy and infection in this series.

MISCELLANEOUS TREATMENT

In forty-four cases of various allergic conditions, such as asthma, urticaria, and pollen asthma, Boyer[22] investigated the use of propadrine hydrochloride. Four patients stated that the propadrine was inferior to other forms of medication, especially ephedrine. Five felt that propadrine was equally efficacious to previous medication, and thirty-five patients reported their greatest symptomatic improvement occurred from this drug. Clinically, bronchospasm and rhinitis were relieved. There were no side reactions so commonly encountered in the administration of ephedrine. Marked relief, therefore, was obtained without the usual nervousness and insomnia which may follow ephedrine. It was not found necessary to administer sedatives with propadrine hydrochloride.

In the treatment of infection of the upper respiratory tract Parkinson[23] recommends the use of the lateral head-low posture while introducing ephedrine in saline solutions into the nose. This is a most efficacious method of producing a shrinkage of the ostia of the sinuses and hence the establishment of drainage of secretion. The method is also useful in the treatment of nasal allergy in those instances in which local shrinkage is necessary. This treatment is particularly applicable in children.

Of twenty-six carefully selected and studied cases of vasomotor rhinitis, Prickman[24] noted definite relief from the use of histaminase in nine, or 34 per cent. In four instances the results were questionable; in the remaining thirteen no relief whatsoever occurred. In patients who obtained relief, the administration of the drug had to be continued, as it did not appear to produce desensitization.

Wilson-Pepper and Royle[25] report a case in which menorrhagia had existed for two years and spasmodic rhinorrhea of considerable severity for eighteen months. Upon injection of the first dose of progesterone the nasal symptoms immediately subsided and did not reappear for several weeks. It is suggested that progesterone warrants further consideration for treatment of rhinorrhea.

At the University of Minnesota, Diehl[26] and his co-workers conducted a three-year study of cold vaccines used on students. Nasal allergy and

sinus infections were excluded. The conclusions may be summarized as follows: The group receiving vaccine subcutaneously experienced an average of 25 per cent fewer colds per person than did the control group. The difference is considered of no importance, however, because a reduction of 25 per cent is not sufficiently great to justify the time and expense in giving the treatment. The group which received a polyvalent vaccine orally experienced just as many colds as the control group. Although the data presented are not conclusive, there is no evidence in this study either that the vaccines reduce the complications of colds or that the condition of the nose and throat is related to the frequency of colds in the cold-susceptible group.

The controlled study of cold vaccines by Hanser and Hanser[27] was conducted on a series of 369 students at the University of Michigan. The following conclusions were drawn: Over 66 per cent of subjects who received placebos stated that they had fewer colds than during the year preceding the experiment. Of the persons who received vaccine intradermally, over 64 per cent considered themselves similarly improved. Of those who received the vaccine subcutaneously, 80 per cent reported fewer colds than during the preceding year. Although the proportion of subjects reporting improvement was greatest in the group in which the vaccine was given subcutaneously, the percentage of difference between the three groups was considered within the limits of possible error.

The results obtained in nasal ionization in seventy-two cases of hay fever were reported by King.[28] Among twenty-four patients with autumnal hay fever, four had complete relief, nine were improved, and eleven had no relief. In nineteen patients with spring hay fever, five had complete relief, ten improvement, and four no benefit. Among thirty-two patients with perennial nasal allergy, six were relieved, fourteen were improved, and twelve had no relief. In summarizing the entire group, it is significant that fifteen patients had relief, thirty-three improvement, and twenty-seven no relief.

HEADACHE

Gittins[29] points out that in most instances of headache only subjective symptoms are present, with no objective evidence to further a diagnosis. Transient disturbances of vasomotor origin in the brain, meninges, ganglia, or nerve sheaths, whether spoken of as migrainous, allergic, or functional upsets, are responsible, he states, for the symptom complex in most instances.

In discussing the various symptom complexes associated with headache, Gittins emphasizes that real pathologic changes in the nose, sinuses, brain, or other part of the head cannot be responsible for such systematic reproduction of similar explosive phenomena over long periods, with intervening periods of good health.

Among other conditions which may cause headache, the possibility of allergy is also emphasized by Gittins. He further states that "spontaneous relief, temporary or permanent, of periodic headache or neuralgia with associated symptoms of vasomotor or allergic origin is more common than is similar relief from the combination of all treatments and operations in the otolaryngologic field and all other branches of medical practice."

ESOPHAGEAL AND BRONCHOSCOPIC ASPECTS

Withers[30] reports a very interesting case of gastrointestinal allergy in which there was involvement of the esophagus. The patient complained of periodic attacks of difficulty in swallowing, pain, bloating, and belching. The patient also had nasal allergy. At first the attacks were mild and occurred irregularly at five- to seven-day intervals. Upon avoidance of the causative foods the patient remained symptom-free for more than two weeks. Several foods were found to reproduce symptoms. The severity of the attacks could be markedly relieved by the ingestion of 0.25 gm. ephedrine. It was not definitely determined whether the obstructive symptoms were caused by spasm or by edema of the esophageal mucosa.

Lockwood[31] points out that primary carcinoma of the bronchus is not a rare disease; it comprises from 6 to 8 per cent of all carcinomas. In frequency it ranks next to malignancies of the gastrointestinal tract. Emphasis is placed upon the careful examination of the sputum of patients with tumor tissue or cells. Many of these patients present symptoms simulating asthma. Wheezing is a common symptom of partial obstruction to a bronchus and is continuous, being influenced by cough and deep inspiration, and often it is not noticed by the patient. Bronchoscopic examination for purposes of inspection and the removal of secretions and tissue for microscopic diagnosis plays an important part in the management of these cases.

Andrews[32] states that the value of bronchoscopy in bronchial asthma is threefold—as a diagnostic method, as a means of aspiration of secretions for vaccines, and as a therapeutic measure. He further states that bronchoscopy is of diagnostic value in bronchial asthma because it is a means of determining the type of tracheobronchial changes and of differentiating asthma from other simulating conditions. He found that vaccines prepared from bronchoscopically aspirated secretions were more satisfactory than ordinary sputum vaccines. In certain cases, definite improvement followed the aspiration of secretions. He feels, however, that bronchoscopic therapy is a symptomatic method of treatment and is only an adjunct to allergic management.

Andrews makes no reference to the cytologic study of the secretions from the tracheobronchial tree. In studies of this type, the cytologic

examination of the secretions should be correlated with other findings. In certain cases accurate diagnosis may be dependent entirely upon cytologic findings.

ALLERGY OF THE EYE AND EAR

Upon a careful search of the literature Parkhurst and Lukens[33] could find reports of only three cases of dermatitis caused by butyn. They add a fourth case of a patient, aged 49 years, in which 2 per cent butyn was used in the eye as a local anesthetic. The next day the patient had a marked swelling and itching of both eyelids on the right side. The following day there was a more severe dermatitis of the lids, with vesiculation and edema; the eye was swollen shut. An erythematous vesicular streak, about 5 mm. wide, extended down the cheek to the chin, apparently following the path along which the solution had run. A positive patch test was noted twenty-four hours after application of butyn to the skin of the arm. The opinion was expressed that such instances of sensitivity to butyn occur more frequently than the paucity of reports would seem to indicate. A case of sensitivity to butyn of a similar nature came under our observation only recently. The skin of the eyelids on both sides was markedly involved with a dermatitis. Eyedrops containing butyn had been used. A positive patch test was demonstrated.

Annenberg[34] reports six cases in which corneal lesions followed the cutting of weeds. Five of the patients complained of pain, redness, itching, and the sensation of a foreign body in the eyes. The palpebral and bulbar conjunctivae showed redness but no corneal involvement. From two to four days later, however, grayish areas of infiltration appeared in the cornea. These reactions lasted several days. Pigweed was found to be the offending factor. One of the patients had other manifestations of allergy. Treatment consisted of the daily injection of foreign protein.

Sjögren[35] reports a case in which the patient, after contact with a certain kind of wood, developed an attack of unilateral nasal obstruction and contemporaneous edema of the eyelid, chemosis of the conjunctiva, transitory myopia of 3.75 D. in association with shallowing of the anterior chamber and a considerable diminution of intraocular pressure. The emptying of the anterior chamber consequently caused a projection of the iris-lens diaphragm.

A woman aged 56 years, reported upon by Granstrom and Nylen,[36] had had repeated attacks of Ménière's disease for several years and also attacks of palpebral edema of the angioneurotic type, accompanied by iritis-like attacks of short duration. This latter was considered as "an intraocular edema of Quincke," and the attacks of Ménière's disease were thought to be an analogous process in the labyrinth. All the symptoms were considered allergic in nature, although the offending allergen

was not found. The examination of the function of the labyrinth and cochlea showed normal findings between attacks. During the attacks, vertigo, rotary-horizontal nystagmus on change of position of the head, and a marked reduction of hearing in the left ear developed.

Jones[37] discusses the occurrence of an allergic type of otitis media. In one instance a child was found sensitive to chocolate, nuts, and wheat. The attack was induced by the ingestion of nuts. In a patient with chronic allergic labyrinthitis, the symptoms disappeared upon the elimination of milk.

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Society Proceedings

SYMPOSIUM ON ALLERGIC DERMATOSES*

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(Continued from issue of November, 1939, p. 65.)

Infantile Eczema. RUDOLPH HECHT, Chicago, Ill.

A definition of infantile eczema is indeed difficult. By the word "infant" one usually means a child under the age of 2 years. Since infantile eczema is not a well-defined condition, classification is difficult and differentiation of one type from another is practically impossible. Furthermore, the condition may present varying phases at varying times, and in many cases several conditions may be present at the same time.

Sulzberger and Hill have done much to clarify our concept of infantile eczema. Thus, Hill has subclassified the group into: seborrheic dermatitis, contact dermatitis, eczematous fungus eruptions, and atopic dermatitis. Several other less common dermatoses may also be included but need no discussion here. Any one or more of the above may be present in the same individual, and one form may be transformed into another type. It is impossible to discuss here the clinical characteristics or the diagnostic criteria. Suffice it to say that the seborrheic type usually occurs in overfed breast-fed infants and presents a greasy scaling eruption frequently involving the scalp. The contact type involves exposed areas and is rare in infants. The eczematoid fungus type has a raised vesicular border with a tendency to peripheral spread and central clearing and is more prone to involve areas other than the face. The atopic type involves usually the face and neck (and in older children may present the typical flexural distribution) and is associated usually with violent itching. It is not uncommon for the seborrheic and atopic types to be present in the same individual at the same time.

When the history, appearance, distribution, and course of the eruption are characteristic, the diagnosis is relatively easy. The differentiation of the various types from one another is sometimes impossible.

There are several important things which characterize the reaction of the infant's skin. First and foremost is the tendency to vesiculate. Each of the four subgroups mentioned may present a vesicular eruption. Examples which demonstrate this tendency to vesiculation are the occurrence in infants of vesicular, bullous, or even pemphigoid

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secondary syphilids. This is unknown in adults. The same holds true for impetigo. This tendency to vesiculation is probably due to the greater permeability of the infantile skin.

Not only is there this greater permeability from within outward, but also a greater permeability from without inward. Thus, it has been demonstrated that an atopic infant's skin is permeable to the application of protein allergens and may react to patch tests with these substances.* Not only may there be these local effects from application of protein allergens, but there may be also absorption of these substances through the skin, resulting in general reactions and even focal reactions at a distance with little or no local effect. Such reactions are unusual in adults.

In the rest of my discussion I shall limit myself to infantile atopic dermatitis. The diagnosis is based on a family history of atopy, the presence of classical immediate wheal-type reactions to scratch or intracutaneous tests with the usual atopens, negative patch tests with the usual contact substances, the presence of reagins in the serum, and eosinophilia. Morphologically, there is an erythematous, papulourticarial, vesicular, frequently weeping eruption usually occurring on the face and neck and characteristically accompanied by violent uncontrollable itching.

Many interesting observations have been made. Among the most interesting is the peculiar reaction to egg white. The majority of infants with atopic dermatitis give a positive reaction to scratch or intracutaneous tests with egg white (Sulzberger and Hill). Even positive reactions to mere local application of egg white have been reported (Moro).

As the child grows older, this reaction may disappear, but in some, of course, it persists. In adults with atopic dermatitis a positive skin test with egg white is comparatively uncommon. The route of sensitization has been explained as occurring via the placenta (Bret Ratner) or via the mother's milk (Donnally) in these infants who have as yet not ingested egg.

I should like to mention some work that we have been doing in the department of Physiological Chemistry at the University of Illinois College of Medicine which may explain some of these peculiar reactions. We have evidence which seems to indicate that ragweed pollen solutions, as ordinarily prepared, contain two types of molecular aggregates, namely, large and small. The data at hand would suggest that the latter sensitize the skin and are responsible for the usual skin tests; while the former may cause the constitutional effects. Theoretically, the small molecules should more easily pass the placental barrier and enter the circulation of the infant. This should also be true of the breast. Thus, these infants may have received

*Peck and Salomon, Rostenberg and Sulzberger, and Moro.

relatively large doses of the small skin-sensitizing molecules and small doses of the large symptom-producing molecules. If this is true, positive skin tests with egg white should be frequent even in an infant who has not as yet ingested egg white.

Some years ago, in a series of unpublished experiments performed with Dr. Arthur G. Cole at the University of Illinois, we skin-tested with various purified fractions of egg white a group of older children and adults who had previously reacted positively to tests with whole egg white. Practically all of these people reacted to the noncoagulable (mucoid), probably relatively small fraction, while the reactions to any one of the other fractions was less frequent.

In the infant less than 1 year of age, we have found a careful history to be invaluable. In these cases, our experience has been that empirical careful environmental control and diet elimination are sufficient in most cases. In older children eating a more varied diet and with more environmental contacts, skin tests may be of definite value in giving leads to the proper etiological diagnosis. Hill is a firm believer in the value of skin tests in these cases.

Much evidence has accumulated in recent years which indicates that environmental substances play a significant role in infantile eczema. Thus, it has been shown that sensitization to house dust and feathers may be frequent in these patients (Peck and Salomon, and Hill). It has been shown that removal of environmental substances plus food elimination offers greater possibilities than just food elimination alone. We always give specific directions for environmental control. We attempt to make the room as "bare as a barracks." We frequently visit the home to check up on the thoroughness of the environmental control.

In attempting to establish an etiological diagnosis, the value of repeated detailed history taking and the cooperation and observations of an intelligent mother or nurse cannot be stressed too greatly.

Regardless of how much we have learned from the immunologic approach and how valuable it may be in some cases, I cannot help but still feel that, at present, the best method of treatment is careful dermatologic management; in other words, if I were limited to one method of treatment, I should choose local treatment.

In addition to the immunologic management one must consider the choice of the proper local remedies, the choice of the proper concentration of remedies, indicated alterations in concentrations of remedies, proper application and removal of remedies (the latter cannot be too greatly stressed), bandaging, careful splinting to prevent scratching, avoidance of soap, the use of sedatives, and general hygienic and medical care.

DISCUSSION

DR. WILLIAM F. MITCHELL, Columbus, Ohio.—In a recent paper concerning infantile atopic eczema the writers cited cases in which they could produce generalized eczema by applying known aggravating substances to isolated eczematous patches. The irritants (wool or feathers in the cases mentioned) were applied, for example, to the cubital spaces when the rest of the skin was fairly clear. The usual intradermal and patch tests had been negative. Have you done any work along this line, or have you any comment to offer?

DR. HECHT.—Dr. Osborne and Dr. Walker of Buffalo published that work in the Archives of Dermatology. They found that wool, not only when applied to the site of eruption, but also when applied to a normal skin area, resulted in a reaction at the site of eczema. Dr. Sulzberger had previously explained this interesting phenomenon by what he calls transepidermal penetration, namely, that the application of a substance (even a protein allergen) to the skin results in its penetration through the epidermis down to the vessels of the cutis (which are the important shock tissues here) and its subsequent distribution to the site of reaction, even far removed from the place of contact, without a local reaction.

DR. MITCHELL.—Is it generally practical as a test?

DR. HECHT.—We have not used it as such.

DR. SULZBERGER.—I have never used this method, but I do not think it can be as conclusive as the environmental elimination of those substances. It is very hard to judge and evaluate the reactions produced when one tests an area which is already affected.

DR. GEORGE L. WALDBOTT, Detroit.—How often do you find purely atopic eczema complicated by such conditions as fungus infection, staphylococcic infection, and contact dermatitis, and how important is it to consider this in your treatment? I wonder if it would be possible at some time this afternoon to teach us something about dermatologic treatment of these conditions—I mean local treatment.

DR. HECHT.—May I answer your second question first?

It was over two years ago that I decided I wanted to learn a little about these allergic dermatoses. I had been practicing allergy for some time previously and was frequently baffled by the allergic dermatoses. I went to New York and said to Dr. Sulzberger, "I should like to spend a couple of weeks with you to learn something about the dermatoses." That was two years ago. I am still associated with Dr. Sulzberger, and I still feel deficient in my ability to diagnose and treat these conditions.

I did not understand the first question quite clearly—secondary fungus and staphylococcic infections? I do not recall having seen a fungus infection complicating an atopic dermatitis. Impetigo may complicate atopic dermatitis. However, seborrheic dermatitis will frequently accompany an atopic dermatitis in infants. Where it is associated with the atopic type in infants the scalp is frequently involved. There are greasy scales on the scalp which you do not usually find in the adult atopic type.

Contact dermatitis may be associated with atopic dermatitis and may be caused by the use of local remedies or by the mother's or nurse's cosmetics, etc., to which the child has become sensitized.

Dr. Sulzberger answered that question on the association of contact and atopic dermatitis and whether or not the two can occur together.

Dr. McKinley London, Cleveland.—Why do they not occur more often?

Dr. Hecht.—I do not know the explanation, but I do know that they rarely occur together. An individual with atopic dermatitis is no more prone to develop contact dermatitis than a normal individual; that is, the incidence of contact dermatitis in individuals with atopic dermatitis is no greater than that of the average population.

Dr. London.—We know that trauma or previous dermatitis is likely to make one polyvalently sensitive. One finds skin trauma in infantile eczema over a comparatively long period of time. Why do not these children develop contact dermatitis more frequently?

Dr. Sulzberger.—Dr. Hecht, shall I try to answer the last question?

In a strictly scientific sense, infantile eczema really should not be called "infantile eczema." It evidences little or no relation immunologically or pathogenically to the contact-type of dermatitis which one usually calls eczema. While it is true that both are generally based on specific sensitization mechanisms and, thus, in some way are distantly related, contact-type dermatitis and infantile eczema are not related in any other way; therefore, immunologically there is no reason why an individual with an atopic type of sensitivity and with a history of infantile eczema should be more prone to contact-type dermatitis than a normal person; nor is there any proof that an individual of atopic constitution should be more prone than a normal person to develop a contact-type eczema. There is no reason immunologically why contact-type dermatitis should be more common in atopic babies.

Now, as to the question of penetration, I think that it is true that atopic dermatitis patients occasionally become sensitized to the medicaments applied to the affected areas. They very often are irritated by the topical agents and probably sometimes become sensitized to some of them. The question is, how much penetration actually takes place when a medicament is placed on an inflamed or exuding area? The penetration is probably not as great as one might at first suppose, because the applied substances tend to be thrown off; that is, the defense mechanisms of scaling, oozing, etc., both dilute and throw off the applied agents. So, applying a remedy in treatment is not exactly like applying an agent and keeping it on a normal skin; nor is it exactly like scarifying an area deliberately and rubbing something into the site.

Does that answer your question?

Dr. London.—Not entirely.

Dr. Samuel M. Peck, New York.—At my suggestion such a piece of experimental work has been done. We were interested in determining just how fragile capillaries were in infants and younger children.

We were very surprised to note that not only prematures but even newborn children had fragile capillaries which could be demonstrated if proper capillary fragility tests were made. The best demonstration was brought about by the use of the intradermal venom test. Gradually, as the infant became older, this capillary fragility was lost. We did not carry the work far enough in the age groups to find out at just what age the condition of the capillaries approached that of the normal child, that is the older child.

In Bruno Bloch's clinic in Zurich they were also interested in the question of the permeability of the skin in infants and children. They approached the problem by doing routine patch tests with a number of routine eczematogenous substances such as formaldehyde, mercury, adhesive, witch hazel, etc., in proper concentrations. I think that it definitely proved that the skins of the children were no more sensitive as far as the thresholds of the elicitation of hypersensitivity were concerned than were those of adults. It must be remembered, therefore, that in very young children, especially of the infantile group, we are not dealing with delicate skins or skins in which the keratin layer is more permeable to common eczematogens; but, in the first few months of life, we are likely to be dealing with more permeable and more fragile capillaries.

Atopic Dermatitis. BEN Z. RAPPAPORT, M.D., Chicago, Ill.

Dr. Hecht has brought out the characteristics of infantile eczema. The morphologic characteristics of the childhood and adult types of atopic dermatitis differ from the infantile type. The childhood and adult types merge, one into the other, morphologically. The lesions are no longer vesicular and develop in definite areas of predilection: the forehead, scalp, sides of the neck, the wrists, and the flexural areas of the elbows and knees.

The cause of the condition varies in different groups. In a large proportion of cases the condition clears with or without treatment at the age of 2 years, with no later recurrence. In another group of cases, after clearing at the age of 2 years, there is recurrence at about the age of 5 to 7 years. After a variable period of months or years the condition clears up in some, either permanently or with recurrence at puberty. In these latter patients the condition lasts until the twenties or thirties, when, with or without treatment, it clears in most patients. This type of grouping is, of course, quite general. Any combination of these types may occur.

It is helpful to look on atopic dermatitis as comparable in many respects to chronic asthma because of its seasonal variability, its chronicity, its resistance to treatment, its response to environmental control. There is a definite seasonal occurrence or flare-up in many cases, reminiscent of chronic asthma. There is the large group of patients who are worse in the winter, clearing up completely or improving markedly in the summer. These resemble the type of asthma due wholly or largely to environmental substances. Then there are

the summer cases which can be definitely divided in our part of the country into spring, summer, and late summer or fall cases with various combinations in this grouping. I have seen a fairly large number of patients in this group. The occurrence of symptoms at the beginning or exacerbation at the height of the various pollen seasons is as striking as the development of hay fever, and like chronic autumnal pollen asthma, there is the tendency to continue for weeks or months past the period of pollination with gradual improvement and final healing. The majority of patients in this group have concomitant hay fever symptoms and react positively to the pollen by skin test. In some cases, the hay fever symptoms, while definite, are minimal, limited to morning sneezing or stuffiness of the nose.

One cannot escape the impression, in these cases of atopic dermatitis occurring primarily in the summer, or with definite summer exacerbations, that pollen sensitivity is the cause of both the respiratory and skin conditions. The result of treatment in our hands, however, does not fully support this hypothesis. Some of our patients have shown definite improvement following pollen hyposensitization. The results, however, have by no means been uniform, so that the proof that pollen inhalation is the cause of the skin condition in these cases is, in my opinion, by no means complete. I have often thought it curious that, despite occasional constitutional reactions of a respiratory type that have been produced with an overdose of pollen in these cases, I have never seen an exacerbation of the skin condition under such circumstances.

Foods as a cause of atopic dermatitis are more important in the child than in the adult, resembling asthma in another respect. The importance of the immediate wheal type of reaction with the various atopens is controversial. Most patients tested intradermally give multiple positive skin reactions. It is difficult, however, to determine the etiological significance of these skin reactions. In children I have found them of greater value than in adults. The most practical approach for adults is to place the patient in a carefully controlled environment, with unusual care in the way of dust-free precautions, and then to treat the condition by topical means. While I still believe in doing complete skin tests on all these cases, I find complete but empirical environmental control plus local care of greater value than the hopeful but frequently futile removal of various foods and inhalants to which the patient reacts. Elimination diet studies are of importance primarily in childhood.

Finally, despite careful environmental and dietary control, a large proportion of the difficult cases that we see either do not improve sufficiently or have unaccountable recurrences. It is strange to see a patient improve rapidly in a hospital room and then, with practically

identical furniture and food at home, suffer a relapse, only to improve again on hospitalization. There may be many atopens in the home that we have not recognized as causes of trouble. Dr. Sulzberger, for instance, has suggested that dyes in rugs and other fabrics may be of importance.

In conclusion, while this type of dermatitis occurs almost exclusively in atopic individuals, and while brilliant results are occasionally obtained by the usual methods at the disposal of the allergists, there are too many patients with whom the immunologic approach gives poor results. Despite this I still do not believe in putting aside the only means that we have for an etiological approach to the problem. All forms of study, a frequently repeated, careful history, and environmental control must be used in the difficult cases. One must not overlook the possibility that allergens as yet undiscovered may add to the number of successfully solved cases.

DISCUSSION

Dr. Matthew Walzer, Brooklyn.—I am more optimistic about the outlook in atopic neurodermatitis than is Dr. Rappaport and others who have discussed this subject today. I may say that, in our clinic, results with atopic neurodermatitis are on the whole as encouraging as they are with asthma. Our principal method of approach is by the indirect method of testing. It is my belief that an individual who has atopic neurodermatitis has an abnormal skin. Whether the lesion involves the entire body or only part of it, that skin is abnormal and may not respond properly to direct testing.

Our approach, however, is not based entirely upon skin testing, no more than it is in asthma. Sensitivities may occur even when reagins are not present in the blood. Local treatment is cut down to a minimum. The main object is to keep the lesions covered with the simplest medium, such as Lassar's paste, preferably without the salicylic acid.

We have not been impressed with the role of inhalants as a cause of atopic neurodermatitis. I would say, however, that youngsters with atopic neurodermatitis almost invariably have some involvement of the mucous membrane. Hence, one must not disregard inhalants, because of the mucous membrane involvement and because it is necessary to prevent asthma, which may develop at a later date. Nevertheless, inhalants, in my experience, are not the most important consideration in the treatment of atopic neurodermatitis.

The question of patch testing in atopic skin diseases is very confusing. A few years ago Dr. Peck reported positive patch test to feathers in some of these eczema cases. Most of his cases were infants and young children. We are now reporting patch tests which are positive to silk, feathers, cottonseed, corn, ragweed, and other atopens. The active principle which induces these reactions is not the oil. These patch reactions are not the same as those obtained with the oils. The lesion consists of superficial pin-point vesicles which do not coalesce and which become indurated or necrose as do the lesions of the usual type of contact dermatitis. These reactions occur almost exclusively in atopic children. More than 50 per cent of atopic children between

the ages of 4 and 14 years give positive patch test to silk. This reaction is specific. Hypersensitiveness to silk can be induced by repeated cutaneous application of the excitant. Almost as high a percentage of atopic children give a positive patch test to feathers as to silk. Reagin antibodies do not mediate these reactions. For all of these reasons I do not believe that the reactions which we have described are the same as those described by Dr. Peck.

The clinical significance of this type of patch reaction is by no means clear. It occurs just as frequently in hay fever and asthma as it does in eczema. The presence of this type of hypersensitiveness in atopic children makes it important to be cautious in interpreting the significance of positive patch test in atopic patients of that age.

Dr. Joseph Harkavy, New York.—I want to add one more word apropos of passive transfers. One should be just as careful in interpreting passive transfers because patients will give passive transfer reactions to a great many substances for which they have absolutely no clinical hypersensitiveness.

Dr. Samuel M. Peck, New York.—I do not wish to prolong Dr. Walzer's discussion. Let me urge you to be as careful in interpreting positive tests to egg white as you are in interpreting some of the results of the positive patch test. The important thing in interpreting patch tests is to be sure that one is dealing with a sensitivity reaction and not with a reaction of irritation. The interpretation of the positive findings is made correctly only when we compare it with clinical facts.

Dr. Albert H. Rowe, Oakland, Calif.—One of the main advantages of a meeting of allergists from all parts of our country is that opinions formed in one region may need modification by experiences in another area. In California, and also in the Middle West, I believe, there is much atopic dermatitis due to inhalant pollen allergy. I am also assured that other inhalants, such as animal emanations, silk, pyrethrum, glue, kapok, cottonseed, and others through blood-borne allergens absorbed through the respiratory mucous membranes, are responsible for many cases of atopic dermatitis.

In northern California in our cases of atopic dermatitis due to pollen allergy, we have learned that small and frequent doses of the antigens are usually required over long periods of time to obtain good results. When the doses are increased too rapidly before hyposensitization has been established, the dermatitis has increased. Later such increased doses are desirable and gradually become possible in certain patients, especially during the pollen-free seasons. During the seasons, however, coseasonal therapy, even more so than in hay fever, must consist of frequent minute doses. Antigens containing five to ten pollens must be given in doses of 0.1 to 0.2 c.c. of dilutions varying from 1:500,000 to 1:5,000. Daily injections of such small doses, which are found to improve the dermatitis and never to exaggerate the clinical manifestations, may be given for weeks at a time before gradual and carefully watched increases are attempted. Such pollen therapy, moreover, must be specific, even to specific grasses or weeds to which the patient is exposed.

DR. LOUIS SCHWARTZ, New York.—Some of the speakers have placed emphasis on the fact that we must be very careful how we interpret patch tests. I want to emphasize that one must be very careful to know with what he is patching. One of the speakers talked about silk sensitivity. The last speaker spoke about how very specific these reactions to patch tests are. I wish to state in reference to silk sensitivity that there are a great many different kinds of silk, and that they differ from each other chemically.

For instance, there is a wild silk which is taken from the silkworm which feeds on oak trees, and a cultivated silk taken from the silkworms that feed on certain kinds of mulberry, producing a white silk. There is a kind of silk taken from Italian silkworms which feed on another kind of mulberry and produce yellow silk.

In addition to that, the silk that you get in your clothes has been subjected to a great many processes; for instance, in weaving the silk from the silkworm, the cocoons are immersed in hot alkaline solutions to loosen the silk in order to reel it, and when it is "thrown," it is again immersed in alkaline solutions and oils; so when you say "silk sensitivity," you are including a great many different varieties of substances which differ from each other chemically, and this fact must be taken into consideration.

A man may be sensitive to Italian silk that has been "thrown," for example, with cresol as an antimildewing agent, and he may not be sensitive to raw Japanese silk that has not been treated in that way.

DR. A. CAZORT, Little Rock.—Dr. Walker told us in 1919 to beware of overdosage, that these patients with atopic dermatitis do not tolerate the large doses of extract which the usual asthmatics will stand. I think I have seen, many times, cutaneous exacerbations which could not be otherwise explained, coming within four hours after treatment. Treatment with the aqueous extract has resulted in a relatively large number of failures. I believe overdosage has been my greatest error. These patients do not tolerate nearly so much extract during season as they do out of season. Frequently, it has been necessary to stop treatment during season, later to try to desensitize, or hyposensitize, for the next season.

I have used desensitizing pollen treatment in 19 cases for over a period of two years in each. In 5 the treatment has been a complete failure; in 7 the effectiveness is doubtful, since other forms of treatment were being carried out simultaneously; in 7 I think the treatment has been of definite and great benefit.

The antigen does not gain entrance transcutaneously. Repeatedly, in and out of season, I have rubbed the pollen thought to be the principal offender into healed flexural areas without evidence of skin irritation. One patient whom I have seen frequently for six years has been particularly cooperative in making studies both on himself and on his son. Formerly he had large skin reactions—I marked them four-plus, if that means anything—to oak, hickory, and ragweed pollens. He had spring and fall exacerbations of atopic dermatitis, the fall attacks never clearing entirely through the winter. Under no other treatment than appropriate pollen injections, the rash has been kept in complete abeyance and skin reactions have greatly decreased in size. Repeated daily applications of pollens in flexural areas have never caused local exacerbation.

My experiences with these cases agree in most details with those of Dr. Rowe, who has discussed the matter in detail in his book.

DR. SULZBERGER.—Atopic dermatitis is a condition which is extremely common. I am very unfortunate in being obliged to see a great many of these cases. I do not know whether Dr. Walzer's results are better than mine or whether he is more easily satisfied with the results which he gets than I am with those which I get. But I am certainly not satisfied, by and large, with my therapeutic results in many cases of atopic dermatitis.

I venture to say that my results in atopic dermatitis are approximately equivalent to what you gentlemen would get in asthma, if you can imagine asthma in which you find drugs ineffective, in which you can use neither iodides nor adrenalin. And I do not think that is a very satisfactory result to get in any group of cases.

I should say I could show you about 30 patients with atopic dermatitis right now whom nothing in the world we know today has helped. They have been starved, and they have been put in an "allergen-free" environment; they have been treated specifically and nonspecifically; and they have been injected and treated by every method known to physicians today, without any benefit.

In my experience, what happens in 100 cases of atopic dermatitis is something like this: First, about 80 per cent of the patients either get well by themselves, after a certain number of months or years, or they are helped materially by topical treatment and by changes of environment, including hospitalization; about 15 per cent of the patients go on, despite therapy, with longer or shorter remissions which clear up only when they reach the age of 20 years or slightly more; in the remaining 5 per cent of the patients, the dermatitis continues after the age of 20, and these are the real refractory cases. I believe that it is rarely that anybody can help these few cases or give them any permanent relief.

Urticaria. J. GARDNER HOPKINS, M.D., New York, N. Y.

I will challenge Dr. Sulzberger—urticaria is as common a lesion as contact dermatitis, and an important thing to remember is that a wheal is just a symptom. Really the only thing that is common to all wheals is that they probably result from the local release of a histamine-like substance.

Many jump to the conclusion that urticaria means allergy because there are so many well-known examples of allergic urticaria—the food urticarias, the drug urticarias (if we admit that drug reactions are allergy), and similar urticarias caused by proteins inhaled or rubbed into the skin locally.

We speak sometimes rather glibly of the shock tissue, but there seems no real evidence as to what the shock tissue is in urticarias. The surprising thing about them is that, whereas in an eczema (or atopic dermatitis) one can produce a wheal by scratching the substance into the skin, one very often cannot in these urticarias.

We are likely to forget that in other forms of urticaria we have no proof of allergic origin; for instance, the name nettle rash is derived

from the fact that anyone who comes in contact with nettles develops urticaria. Histamine in anybody's skin produces urticaria; galvanic shock produces it, or a mechanical stimulus.

A long time ago it was found that chronic urticaria could be produced by certain animal parasites, especially the *Echinococcus* and the roundworm, and it was thought that these parasites produced toxic substances which caused wheals. The work of Longcope, and Rackemann, I think it was, on the *Echinococcus* urticaria showed that this was allergic, and Jadassohn demonstrated the allergic mechanism in urticaria caused by the *Ascaris*. This was interesting because most other allergic urticarias occur in acute attacks, and our real problems are the chronic urticarias that come on day after day. Here is a type of urticaria where the patient is carrying the antigen, the foreign protein, in his own internal lesions.

The mechanism of urticaria resulting from focal infection is probably similar, although it has never been clearly demonstrated. From a practical standpoint, such urticarias form an important group.

There is still another type that I think Dr. Rackemann would put in his intrinsic class. A good many years ago Gerber reported cases of urticaria occurring during the menstrual period, in which he could produce the wheal by injection of blood taken at that time. This was confirmed by Harrison. We have seen cases, and I think it is clear that these patients carry some substance in their own blood, not a foreign parasite but something entirely autogenous. Can we say they are allergic to it? At any rate, they react with wheals if you introduce it into the skin.

The group of so-called "physical urticarias," due to light, heat, and cold, are of special interest.

As to the mechanism of the local urticarias caused by light and heat, we have, so far as I know, no clue. As to cold, you will recall the work of Harris on cases associated with paroxysmal hemoglobinuria. We found there was a circulating antibody which apparently combined with skin cells at low temperature just as the hemolysin combined with the blood cells. According to his evidence (which I think has never been confirmed), this is a real sensitization, the antigen being some constituent in the skin.

We have tried to confirm the work of Harris in cases of cold urticaria, and others also have tried hemoglobinuria, but without success.

Another thing I will mention, which may be familiar to most of you, is the work of Grant on heat urticaria. This concerns patients who develop generalized urticaria when their body temperature is raised, not those who develop local urticaria in an area to which heat is

applied. In such persons Grant reproduced the eruption by the introduction of choline compounds, either by ionization into the skin, causing the local reaction, or by the hypodermic injection, which produced a generalized reaction.

That at once explains why such patients break out from any cause that produces a discharge of acetylcholine from their cutaneous nerve endings. They break out if their body temperature is raised. They break out with violent exercise, and they will also break out from emotional excitement. Under any of these circumstances, in normal individuals there is a discharge of acetylcholine from the peripheral nerve terminals.

Again, is that allergic? We are tempted to say they are sensitized to this physiologic substance which is in all of our bodies, although as yet we have no proof that one can sensitize to acetylcholine.

We have been interested in the morphology of wheals, but one difficulty is that we do not often see our urticarias. Urticaria is a matter of history. When we do see them, we know that they may be tremendously unlike. We see red wheals and white wheals, gyrate wheals, and little punctate wheals.

One thing interesting about these heat and psychic urticarias is that you can often spot them at sight. The first thing you see is a huge flare, and that is all some patients show, just blotches of red; in the center of that, the really sensitive case will develop little beadlike wheals.

The picture is so characteristic that one may often make a diagnosis on inspection. It seems quite possible that wheals from other causes have characteristics that would identify them if we only knew enough to recognize them.

DISCUSSION

Dr. Leon Unger, Chicago.—I have been puzzled for some time about the difference between urticaria and angioneurotic edema. We know the latter does not itch and has large asymmetrical swellings. I should like to know whether or not there is any fundamental difference between the two conditions.

Dr. Hopkins.—I do not believe there is any fundamental difference because you so often see the two things together. The principal difference is that angioneurotic edema is subcutaneous, and urticaria intracutaneous.

The sensation of itching is due to a stimulus in, not under, the skin. I do not think you see angioneurotic edema in heat urticaria; I never have yet. It is seen very often in cold urticaria and often in bacterial urticaria. In my own experience, I do not think I have ever seen a proved case due to foods, although it is talked about.

DR. UNGER.—It is common in fish cases.

DR. HOPKINS.—I think it is less common than is supposed. A good many patients with angioneurotic edema think it is due to food. It is really due to infection.

DR. SULZBERGER.—Many of them are due to drugs—aspirin, for instance.

DR. HARRY L. HUBER, Chicago.—You spoke of focal infection. Dr. Menagh of Detroit has associated infections of the gall bladder with many of his urticarias. I should like to know what you think of that.

DR. HOPKINS.—Well, Dr. Menagh's percentages were astonishingly high, so high as to make one wonder. However, I do think that focal infections are a very important cause of the chronic urticarias, the persistent, recurrent types.

In our experience we have never proved one to be due to gall bladder infection, but I do not believe that is because it is not common, but merely because it is a difficult mechanism for us to study. Most of the infections in our cases have been teeth or tonsils or infections around the upper respiratory tract.

DR. BENNETT KRAFT, Indianapolis.—I imagine all of us have seen patients who have both hives and asthma, or asthma and neurodermatitis. In some cases of this type, it may be possible to relieve one of the conditions, but not both. Thus, if the patient becomes asthma-free, the hives or neurodermatitis will become worse.

Does anyone here know an explanation of this mechanism?

DR. HOPKINS.—I would want to be sure that was true before I tried to explain it.

DR. KRAFT.—I have seen it.

DR. GEORGE L. WALDBOTT, Detroit.—For some time past I have been particularly interested in urticaria. I have been able to track down a number of patients with urticaria who have had contact five to nine days previously with the materials to which they were clinically sensitive. There is usually a high white blood cell count, a lack of eosinophilia, and a lack of positive skin reactions. I wonder if you have encountered any such cases of chronic urticaria resulting from serum sickness.

DR. HOPKINS.—I should like to ask Dr. Rackemann to answer that.

DR. FRANCIS M. RACKEMANN, Boston.—I would like to make this observation about skin tests in urticaria: In a study of serum disease, there are skin tests and antibodies which do not appear in demonstrable quantities until after the acute process has subsided. It has occurred to me more than once that it is possible that the reason why our skin tests in urticaria fail is that the disease process has not reached its end. If only we could persuade our patients to come back to us in a month or so after the urticaria had subsided, if and when it did, then we might test them and perhaps know a little more and throw a little light upon the subject.

DR. HOPKINS.—I thought everybody knew the answer to that, sir. I think if there is serum sickness, your patient is not sensitive at the time the serum is injected. If your patient is not sensitive, the reaction occurs at the end of the time at which his antibody is developed. If you injected him again, he would react at once, wouldn't he?

DR. SULZBERGER.—Dr. Rackemann, I think I can answer your question. The same idea occurred to me and I tested some of my patients with urticaria proved due to certain foods, performing my tests not only during the attack, but repeating them a month and two months afterward. In my particular cases the patients still did not react to the skin tests.

DR. RACKEMANN.—Theoretically they do not react until the circulating antibody subsides and becomes localized in the tissue of the skin.

DR. SULZBERGER.—Take the strawberry, that notoriously common cause of acute urticaria. I have yet to find a case of strawberry urticaria that reacts to skin tests with strawberries at any times. Has anyone here seen a case with a positive urticarial skin reaction to a skin test with strawberries? And yet the ingestion of the fruit will often produce urticaria in the very same "skin test negative" case.

DR. ROBERT L. BENSON, Portland.—It has been my experience if the strawberries have hot water poured over them to remove the surface, they will not cause urticaria. It is not a specific strawberry urticaria.

DR. MILTON B. COHEN, Cleveland.—I have been very much interested in the bacterial aspect of urticaria. How is one to determine what to do with the cases of hives? What is one to do when he has exhausted all of the possibilities and by inference has arrived at the conclusion that he is dealing with urticaria of bacterial origin? When I see patients with chronic urticaria, I try to find out if they are taking any kind of drugs, and if they are, discontinue the drugs.

I merely want to say I cannot get results in patients forced on me with chronic urticaria, unless by chance I find the urticaria to be due to drugs and occasionally to a food. I am speaking particularly of the type of urticaria that exists independently of any of the other so-called allergic manifestations. I can do something for the cases of urticaria in patients with vasomotor rhinitis, particularly with bronchial symptoms, but I should like to have somebody tell us now how to get some kind of result which justifies the patient with chronic urticaria alone in coming to us.

DR. BEN Z. RAPPAPORT, Chicago.—I have been hesitating to speak of a case that we have studied; I do not speak of it because of its rarity, but with the hope that in the experience of others it may not be a rare cause of urticaria.

A dentist engaged in anatomic research at the University of Illinois had urticaria for several years. To be brief, we found after about fourteen months of study that his urticaria was caused primarily by the cigarettes he was smoking. The glycerin in these was oxidized to acrolein which was one of the causes of his urticaria. When he smoked cigarettes which contained no glycerin, he was free of hives. When

a drop of glycerin was placed on such a cigarette he would have hives after smoking. We were able to predict that if he ate steak broiled over a hot flame, or broiled fish, he would have urticaria because of the oxidation of any fat into acrolein.

In studying this case (and we have not completed the study yet), we have tested with straight chain aldehydes up to 18 carbon atoms. The reactions were marked even in very high dilutions with the shorter chain aldehydes. The longer chain aldehydes were less active up to the one with 18 carbon atoms, with which no reaction was obtained. When, for instance, a drop of a 1:1,000,000 formalin solution was placed on the lip, generalized urticaria would occur in ten minutes. A stronger solution of the higher aliphatic aldehydes was required for such a reaction. It is interesting that, so far, only the straight chain aldehydes have been found active in his case. The aromatic aldehydes so far tried, for example benzaldehyde, produced no hives.

I bring this up, not because it is curious, but because it may be important. If formerly someone had told me, "If I prepare meat by broiling it, it gives me hives, while boiled beef does not do so," I would have thought the patient imaginative and paid no attention to the remark.

Acrolein is a very active aldehyde and is produced in any food containing fat or prepared with fat if sufficient heat is used, as in broiling or frying. Acrolein is related to formaldehyde. We are trying to find some formaldehyde-sensitive patients to discover whether or not they are sensitive to other aldehydes. However, some of you may have access to such patients and may find that aldehyde sensitivity, especially to acrolein, is not rare.

DR. HOPKINS.—I do not know how to answer the question about focal infections. I know of no way to be sure that an infection causes an urticaria unless the infection is cleared up. However, if patients have really bad tonsils or teeth, they ought to come out anyway, and that may rid them of their urticaria.

I am grateful to Dr. Rappaport for introducing something really new into this presentation.

DR. BARNEY A. CREDILLE, Flint, Mich.—I have recently had a patient with an angioneurotic edema which turned out to be a medicolegal case. A man about 50 years of age injured the stump of an amputated leg and it became infected. He then developed the marked swelling of the lips and eyes and, in a short time, edema of the glottis. When I saw him, he was having a severe attack of angioneurotic edema with marked dyspnea, which was relieved with adrenalin.

The plaintiff claims that the infection is responsible for his edema. He gave marked reactions to a large number of allergens, and the edema was controlled with dieting.

The question comes up whether or not the angioneurotic edema was precipitated by the infection.

(Symposium to be continued.)

THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS

Resolution

WHEREAS, the Society for the Study of Asthma and Allied Conditions has learned with deep regret of the death of Dr. George Flamm, and

WHEREAS, the Society has sustained the loss of one of its honored and devoted members, and

WHEREAS, his personality, character, and kindliness were admired by all who knew him, and

WHEREAS, he has made valuable and stimulating contributions in the field of allergy, be it

Resolved, That we, the Society for the Study of Asthma and Allied Conditions, formally and sincerely record our great loss and misfortune in his untimely passing, and be it further

Resolved, That a copy of this resolution be spread upon the minutes of the Society, that a copy be forwarded to his wife and family, and that a notice be printed in the JOURNAL OF ALLERGY.

MATTHEW WALZER
SELIAN HEBALD
A. H. FINEMAN

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

Hay Fever Among Japanese: III. Studies of Atmospheric Pollen in Tokyo and in Kobe. Hara, H. J.: Arch. Otolaryng. **30**: 525, 1939.

The author had previously reported that the Japanese are not racially immune to allergy, as it was shown that 3.5 per cent of the Japanese population of Southern California have hay fever. However, people living in Japan do not suffer from hay fever, although other forms of allergy exist. Pollen studies made by daily exposure of coated glass slides from March, 1936, until November, 1936, in the cities of Tokyo and Kobe, which are located on the main island, showed the quantity of pollen in the air to be small. The pollinating season begins the latter part of March and lasts until the end of May. By far the most numerous of the pollens were those of pine, which are abundant all over the island. This pollen plays virtually no part in the causation of hay fever. Bermuda grass is absent from Japan, while ragweed, which has been unknown, is said to be coming into the country.

Wood Smoke as a Cause of Asthma. Rappaport, B. Z., and Hecht, R.: J. A. M. A. **113**: 1024, 1939.

The case is reported of a fireman who developed attacks of bronchial asthma upon exposure to smoke indoors. Change of duties without contact to wood smoke resulted in a symptom-free period of eight years. Skin tests to wood smoke extract were negative on different occasions. The facts in the case which point to specific hypersensitiveness are the absence of symptoms until taking up his present occupation, the incubation period of eight months before symptoms began upon exposure to wood smoke, the recurrence of an attack with each subsequent exposure, the four-hour interval between exposure and onset of symptoms, the return of symptoms upon the first re-exposure eight years afterward, and the fact that his co-workers were unaffected by similar exposures.

Benzedrine Inhalation in Asthma. Kalmon, M.: Ohio State M. J. **35**: 851, 1939.

Benzedrine base was used by the oral inhalation method to determine its usefulness in relieving asthmatic attacks. Fifty-two asthmatic episodes occurring in ten patients were treated in this way; they were classified according to their severity. In none of the severe attacks was a satisfactory result obtained. A decrease of asthmatic symptoms was noted only in the mild spasms. The effects of benzedrine inhalant are not comparable to those of adrenalin chloride 1:100.

All the patients complained of a mild cough following the oral inhalation of benzedrine, and this was a troublesome symptom in one patient. The vital capacity was increased as noted by the patient's statements.

Theophylline Ethylenediamine (Aminophyllin) in Bronchial Asthma. Efron, B. G., and Everett, P.: New Orleans M. & S. J. **92**: 77, 1939.

The authors are enthusiastic about aminophyllin in bronchial asthma, especially in those cases that are adrenalin-fast. The patient usually experiences prompt

and complete relief from its use, although in some cases only delayed or partial results are obtained. It is not necessary, generally, to give the drug more often than every twenty-four hours. The authors have not observed a single case that became aminophyllin-fast.

The drug is given intravenously, usually in a dose of 7½ grains dissolved in 10 to 20 c.c. of distilled water. It is slowly injected and extravasation into the subcutaneous tissue should be avoided. Unpleasant reactions occur fairly frequently, but these are usually mild and transitory.

Further Observations on Allergy to Smuts. Wittich, F. W.: Journal Lancet **59**: 382, 1939.

The author emphasizes the marked incidence of smut spores in the air of Minnesota and the Northwest. These spores originate mainly from the infected grain and particularly from wheat. They are most abundant from July to November. He believes that smuts are responsible for a great deal of the allergic manifestations in these areas. Of 105 patients with respiratory allergy whose history warranted testing for fungi, 52 had asthma, 26 had hay fever, and 27 had both. Of this number, 56 per cent reacted to pollen, 42 per cent to animal danders and miscellaneous inhalants, 23 per cent to common air molds, 23 per cent to smuts, and 10 per cent to yeast. Of the 24 patients reacting to smuts, only 5 failed to react to other fungi. Primary smut allergy was present in probably eight cases. In smut allergy the author observed a tendency for the patient to react to the host grain from which the smut originated. Desensitization with smut extracts yielded satisfactory results.

The Use of the Low Temperature Ball Mill for the Preparation of Pollen Extracts. Eagle, H., Arbesman, C., and Winkenwerder, W. L.: Bull. Johns Hopkins Hosp. **65**: 283, 1939.

The authors ground pollen of short ragweed, timothy, orchard grass, and English plantain in a special ball mill kept at a temperature of -80° C. By such a method more than 90 per cent of the pollen is effectively broken. While there was a higher total nitrogen and higher protein fraction than in extracts obtained by the ordinary methods, immunologic and clinical studies failed to show any appreciable differences.

Asthmatoid Heart Failure: A Form of Left Ventricular Failure and Its Differentiation From Bronchial Asthma by Circulation Time and Other Criteria. Plotz, M.: Ann. Int. Med. **13**: 151, 1939.

The usual methods of differentiating between bronchial and cardiac asthma are not always reliable. The author finds that a study of the circulation time is the best method of differentiation. In the cardiac disease the circulation times show decreased velocity in the pulmonary circuit. In allergic asthma the velocity of the circulation is actually increased. One way of measuring the left heart time is to subtract the arm-to-lung time (intravenous injection of 0.3 c.c. ether with 0.3 c.c. salt solution) from the total circulation time (sodium cyanide).

The Use of CO_2 Inhalation as a Test of Circulation Time. Gubner, R., Schnur, S., and Crawford, J. H.: J. Clin. Investigation **18**: 395, 1939.

The authors employed CO_2 to test circulation time in a group of patients with heart disease, some of whom had left heart failure. A series of normal persons and another group of four asthmatic patients without cardiac defects were

tested. The method is harmless and has the advantage of directly measuring "left heart time." Other methods are indirect and require two injections. The patient is instructed to take two deep inhalations of the gas (50 per cent CO_2) through the mouth. The end point is felt as a sensation of warmth passing over the head, and objectively it is noted by a quickening and deepening of the respiration which can be recorded.

The normal "left heart" circulation time ranged from 5 to 10 seconds, the majority being 7 to 8 seconds. In those patients with cardiac failure, the time was increased, the increase being commensurate with the degree of left heart failure. The four asthmatic patients without heart disease had normal values for circulation time.

The Use of Histamine and Histaminase in the Treatment of Allergic Reaction to Insulin. Roth, G. M., and Rynearson, E. H.: Proc. Staff Meet., Mayo Clin. **14**: 353, 1939.

In a case in which insulin caused marked local and respiratory allergic reactions, histaminase effectively prevented the reactions. Not all batches of histaminase were efficient. Small doses of histamine in increasing amounts given twice daily were also effective.

Altogether, the authors used histaminase in twelve cases of insulin allergy with varying results.

Psychogenic Factors in Asthma. French, T. M.: Am. J. Psychiat. **96**: 87, 1939.

The conclusions arrived at in this report are based upon analyses of twenty-four cases of bronchial asthma. Superficial examination showed a considerable divergence in the personality pictures of the patients, but it was determined that the acute asthmatic attack occurred following a temptation, which, in all the instances cited here, was sexual and interfered with the patient's bond to the mother (Oedipus complex). It is the temptation rather than the gratification which usually serves as the precipitating cause of the asthmatic attack. The defenses by means of which the ego is able to protect itself from the asthmatic attack are: (1) confession of the temptation; (2) gratification in the sexual act; or (3) attempts on the patient's part to withdraw from the whole temptation situation by means of autoerotic substitutes.

Potassium in Allergy. Bloom, B., and Grauman, S. J.: Southwestern Med. **23**: 205, 1939.

Good results with potassium salts taken orally in the treatment of allergy continue to be reported by the authors. The present paper adds more cases and

RESULTS OF TREATMENT

	IMPROVED	UNIMPROVED
Hay fever	48	4
Hay fever and pollen asthma	7	2
Chronic allergic sinusitis	13	7
Nasal mucous polyps	4	3
Chronic asthma	2	27
Acute urticaria	7	1
Chronic urticaria	2	1
Angioneurotic edema	2	0
Chronic eczema	5	3
Migraine	2	6

stresses two facts: first, that untoward effects may occur in asthma; and second, that larger doses than were originally thought are sometimes necessary in hay fever. In some of the patients potassium chloride increased the symptoms.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Histaminase in the Treatment of Urticaria and Atopic Dermatitis: A Preliminary Report. Laymon, C. W., and Cumming, H.: J. Invest. Dermat. 2: 301, 1939.

After reviewing previous fundamental work on histaminase and past attempts to use histaminase in the treatment of various allergic dermatoses, the authors describe their results in seventeen cases of urticaria, two cases of urticaria factitia, and eight cases of atopic dermatitis. The histaminase was administered both by intramuscular injections one to three times weekly and by mouth in doses of two or three tablets three times daily. No unfavorable reactions to the drug were noted.

The patients with urticaria did not include any in whom the disease had lasted for less than several weeks. Cases were selected for study only when the cause of the eruption could not be determined and when the usual therapeutic measures had been unsuccessful. About 60 per cent of the patients with urticaria were cured in an average time of ten days; 10 per cent were improved; and 30 per cent were unimproved.

The two cases of urticaria factitia showed no change after three and six weeks of treatment, respectively. There was likewise no improvement in any of the eight patients with atopic dermatitis.

The authors conclude that histaminase is a useful adjunct to other therapeutic measures in urticaria.

Nails and Nail Changes: I. Investigation of Nail Lacquers and Their Components. Silver, H., and Chiego, B.: J. Invest. Dermat. 2: 361, 1939.

An investigation of the toxicity for albino rats of two nail lacquers demonstrated that these substances were definitely nontoxic. Attempts to sensitize guinea pigs to nail lacquer and various concentrations of brilliant green dye both by means of intradermal injections and topical applications were uniformly negative.

The authors then performed a large series of patch tests on sixty-two persons (both normal patients and patients with various skin diseases). The substances tested included various lacquers, dyes, solvents, polish removers, and perfumes. In no instance was there a reaction to a finished nail enamel, although there were a few very mild reactions obtained with the dyes. These findings suggest to the authors that "dyes enmeshed in lacquers become relatively innocuous."

Thiocyanate Dermatitis. Green, N. E., and Snow, J. S.: Arch. Int. Med. 64: 579, 1939.

The patient reported on was given thiocyanate for hypertension. There was a past history of urticaria in childhood, migraine in early adult life, and sensitivity to aspirin. Seven days after thiocyanate therapy was started, at a time when 4.55 gm. of the drug had been ingested, an itching eruption appeared on

the back. At first there were only erythematous maculopapules and follicular papules on the thighs, buttocks, and back. Later large urticarial wheals appeared, and the eruption became generalized. Accompanying the eruption there were fever, conjunctivitis, sore throat, dysphagia, pleuritic pain, and several attacks of asthma. Generalized exfoliation occurred after about two weeks. The reaction occurred when the blood level of thiocyanate was well below that at which toxic symptoms may be expected. It is presumed, therefore, that the reaction was allergic in nature.

Diagnosis of Hypersensitiveness to the Bee and to the Mosquito, with Report of Successful Specific Treatment. Benson, R. L.: Arch. Int. Med. **64**: 1306, 1939.

The author reports instances of extreme sensitiveness to the sting of the honeybee and to the bite of the mosquito. The reaction in each instance consisted of an immediate wheal followed by a painful, red, infiltrated, late reaction which persisted for several days. With both species of insect it was found that the hypersensitivity was directed, not toward the venom or saliva, but toward water-soluble antigens present in the bodies of the insects. Local reinoculation of these antigens abolished the late reaction locally but had no effect on the immediate wheal reaction. Passive transference was demonstrated for bee extract.

The repeated injection of extract of mosquito or bee in several instances resulted in desensitization to the bites of bees or mosquitoes in so far as the late reaction was concerned. The immediate wheal reaction was not changed. The cases reported in the paper indicate that desensitization is sometimes achieved with relatively few injections.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

The Effect of Hypophysectomy on Immunity and Hypersensitivity in Rats With a Brief Description of the Operative Technic. Molomut, N.: J. Immunol. **37**: 113, 1939.

A simple and rapid technique for total hypophysectomy in rats and guinea pigs is described. With this technique the effect of hypophysectomy on antibody formation in rats and on their susceptibility to anaphylaxis was studied.

Using sheep red blood cells, crystalline ovalbumen, and normal horse serum as antigens, the author found that complete ablation of the hypophysis in rats did not materially affect antibody production (hemolysin, precipitin). The time interval after removal of the hypophysis did not seem to have any bearing on the antibody titers.

Rats, sensitized by three intra-abdominal injections of 1 c.c. of normal horse serum given every third day, were shocked on the eleventh day after the last sensitizing injection by the intravenous administration of 1 c.c. of the specific antigen. Fatal active anaphylactic shock was produced in twenty-four of forty-nine hypophysectomized rats. The majority of the remaining twenty-five had anaphylactic symptoms to a variable degree. Of the thirty-nine nonoperated, sensitized controls, only nine showed mild or moderate anaphylactic symptoms. Anaphylactic shock was most common in rats hypophysectomized forty-seven days prior to the administration of the shocking dose, indicating that the longer the time interval after removal of the hypophysis, the greater the susceptibility to the shock dose.

In a small series, the author also demonstrated typical anaphylactic shock and autopsy findings in three hypophysectomized rats sensitized with alum-precipitated ovalbumin. Of ten sensitized, nonoperated controls, none died, and six exhibited some evidences of shock.

Allergy in Brucella Infections. Morales-Otero, P., and Gonzaléz, L. M.: Proc. Soc. Exper. Biol. & Med. **40**: 100, 1939.

Cutaneous hypersensitiveness to *Brucella* and other immunologic reactions, such as agglutination, complement fixation, and opsonocytophagic index, were investigated among 212 milkers and cattle handlers in a region where endemic abortion in cattle was prevalent.

One-tenth cubic centimeter of a purified protein antigen prepared from *Brucella* and diluted with saline so that it contained 0.1 mg. nitrogen per cubic centimeter was used for intracutaneous testing. A reading was made in forty-eight hours. A positive reaction consisted of marked erythema and induration. As a rule, the area of edema was much larger than the erythematous area. Constitutional reactions, manifested by general malaise and slight fever, occasionally occurred.

Of the 212 cases tested, 7 (3.3 per cent) showed positive complement fixation, 5 (2.3 per cent) positive agglutination, 46 (21.7 per cent) positive opsonocytophagic reactions, and 63 (29.6 per cent) showed cutaneous hypersensitiveness to *Brucella* antigen. Of all the persons tested, 3.3 per cent had a history of undulent fever. Three of seven persons working in the authors' laboratory showed positive cutaneous reactions. These three workers were the only ones in the series who had handled *Brucella* cultures. They had never shown signs or symptoms of the disease.

The results indicated that there was no correlation between cutaneous hypersensitiveness to *Brucella* and other immunologic reactions to the same antigen. Contact with infected material evidently resulted in the development of a state of hypersensitiveness without clinical evidence of the disease.

The cutaneous reaction to *Brucella*, therefore, does not necessarily indicate past or present infection, since hypersensitiveness may develop in persons who have had close contact with the infected material.

The Blood Histamine During Anaphylactic Shock in the Horse and Calf. Code, C. F., and Hester, H. R.: Am. J. Physiol. **127**: 71, 1939.

A modification of the Barsoum and Gaddum technique was employed to study alterations in the histamine content of the blood during anaphylactic shock in the horse and calf.

Two horses were sensitized by twelve daily intravenous injections of 45 c.c. of dog serum. Two other animals were sensitized by alternating intravenous and subcutaneous injections of from 40 to 50 c.c. of egg white administered daily. A shocking dose of from 100 to 500 c.c. of the specific antigen was administered intravenously after a three-week interval. The intravenous injection of 100 c.c. of dog serum in normal control horses produced no reaction. The intravenous injection of 500 c.c. of egg white in the normal animal produced a mild reaction with a transient negligible fall in the blood histamine content. The anaphylactic symptoms in the horse consisted of increased peristalsis, marked sweating, and progressive respiratory dyspnea. In one instance, anaphylactic death occurred within eight minutes following the injection of the shock dose of egg white. During anaphylactic shock the histamine content of the blood decreased in two animals as compared with normal control values, and in two instances it completely disappeared from the blood.

Four calves, sensitized by six alternating intravenous and subcutaneous injections of horse serum or egg white, were shocked from five to seven weeks later. Anaphylactic symptoms consisted of increased panting-like respirations and gradual distention of the abdomen which became very marked. Two of the animals, shocked while under anesthesia, responded with similar symptoms. The distention of the abdomen was shown to be due to marked gaseous dilatation of the stomach. The histamine content of the blood during anaphylactic shock was found to be reduced in two animals and completely absent in two.

The authors were unable to produce sensitization in sheep and goats.

In both the horse and the calf the marked reduction in the histamine content of the blood during anaphylactic shock is in marked contrast to the increased liberation of histamine in the blood during severe anaphylactic shock in guinea pigs and dogs as reported by Code.

Sensitization to Tuberculin Produced in Children by Heat-Killed Tubercle Bacilli.
Flahiff, E. W.: Am. J. Hyg. **30**: 65, 1939.

The artificial production of sensitization to tuberculin in children was investigated.

One hundred and thirty-eight children were studied. All were negative to tuberculin tests with O.T. up to 1.0 mg., and all had negative chest roentgenograms. They lived in a school where no tuberculosis was evident in the other 228 children, who exhibited positive cutaneous tuberculin reactions. Sixty-six of the one hundred and thirty-eight children were used as controls. The other seventy-two were given five intracutaneous injections at one-week intervals of 0.1 c.c. saline containing 1 mg. of heat-killed tubercle bacilli derived from a virulent bovine strain. If the local edema following an injection reached 10 mm. in diameter, the injections were discontinued. Cutaneous tests with from 0.01 mg. to 1.0 mg. O.T. were performed at the end of five weeks. If no reaction followed these tests, the subjects were retested four weeks later. If negative findings were then obtained, the sensitizing course of five weekly injections was repeated. The vaccinated and control groups were tuberculin-tested at three-month intervals over a three-year period.

In the vaccinated group, 73.8 per cent of the seventy-eight children showed positive tuberculin reactions at the end of six months, whereas all in the control group remained persistently negative. In most instances, the first five injections were sufficient for sensitization. The induced positive tuberculin reactions were usually maintained over the three-year period of observation.

Tuberculin Patch Test: A Comparison With the Mantoux Intracutaneous Test.
Taylor, G.: Am. Rev. Tuberc. **40**: 236, 1939.

The tuberculin patch test (Vollmer) was compared with the Mantoux intracutaneous test in a series of 744 cases, ranging in age from 3 months to 71 years. Each subject was tested simultaneously with 0.1 c.c. of a 1:1,000 dilution of O.T. intracutaneously on one arm and with the patch test on the other arm. The Mantoux test was read after forty-eight hours, at which time the patch was removed. The patch test was read at seventy-two hours to permit any irritation caused by the adhesive tape to subside.

Of these subjects, 25.7 per cent gave both a positive Mantoux and a positive patch test. In 68.6 per cent of cases both tests were negative. In 3.6 per cent of the subjects a negative Mantoux and a positive patch test were obtained. Of

these twenty-seven subjects, twenty-six were young adults. In 2.0 per cent of cases a negative patch test and a positive Mantoux were obtained. Of these fifteen subjects, twelve were over 50 years of age.

These results indicate that the simple Vollmer patch test is, on the whole, as effective as the Mantoux test. The patch test is slightly more sensitive than the Mantoux test in young adults and is less sensitive in persons past the age of 50 years.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Immunologic Relationship Between Cow's Milk and Goat's Milk. Hill, L. W.: J. Pediat. **15**: 157, 1939.

Cow and goat casein appear to be immunologically similar. There is more species-specificity between cow and goat lactalbumin than there is between the caseins, but they are by no means entirely species-specific. For example, when 44 eczematous infants who gave a positive intracutaneous reaction to cow lactalbumin were tested to goat lactalbumin, ten gave negative reactions, nine reactions were doubtful, and twenty-five were just as positive as they had been to cow lactalbumin. It is suggested that at least two lactalbumin fractions are concerned, one species-specific, the other not, and that a person may be sensitive to one or both. An analagous situation is seen in grass pollen sensitivity.

A group of patients who are apparently sensitive to the species-specific lactalbumin fraction is that group of infants who are shocked by taking cow's milk but who do not have eczema. The majority can take goat milk without trouble and show a negative skin test to both casein and lactalbumin. Twenty-five such instances were collected from the author's cases and the literature. To explain the negative skin test the suggestion is made that the situation in infants may resemble anaphylaxis in animals more than atopy in human beings.

Allergic Enterocolitis With Rectal Prolapse. Ehrlich, M. A.: J. M. A. Georgia **28**: 439, 1939.

Rectal relaxation or prolapse or enterocolitis in infants and children is not infrequently held to be due to allergy. In support of the hypothesis the frequency of positive food reactions by the intradermal method is mentioned. Schloss' studies upon skin tests in normal infants and in those with gastrointestinal disturbance are not mentioned.

The condition is seldom diagnosed except in the southern states, the author says. The comments of numerous allergists throughout the country whose opinions in the matter were sought are summarized. Most of them had not encountered the picture presented.

Objective Assessment of the Allergic Child. Cohen, M.: Ohio State M. J. **35**: 1192, 1939.

Infection, dietary deficiencies, constitutional diseases, and allergy may all disturb the otherwise orderly process of growth and maturation. Allergy, because it is common, operates over a long period of time, and tends to occur during vulnerable early life, is especially apt to do so.

Weight, stature, and maturity are affected in the order named. Fluctuations in weight may go hand in hand with fluctuations in allergic activity.

Skeletal growth, though not as easily influenced as soft tissue growth, is more permanently affected by allergy. In bone, nature does not seem to repair damage previously done or to improve at a later date previous growth insufficiencies. Since allergy tends to occur in early childhood and this is a time when facial bone development should be rapid, interference with growth at this time may lead to permanent facial deformity. The flat, narrow face with high palate and orthodontic deformity often results. The adenoid facies should be called the allergic facies.

Maturation, as indicated by bone age, is usually disturbed only by a severe degree of allergy.

Transitory Lung Infiltrations Associated With Eosinophilia (Löffler's Syndrome). Smith, D. C. W., and Alexander, A. J.: South. M. J. **32**: 267, 1939.

The case of a 7-year-old girl with transitory lung infiltration and eosinophilia of from 30 to 54 per cent is described. The case differs somewhat from the clinical picture described by Löffler in that there were fever and a preceding infection, bronchopneumonia having occurred a month previously. The usual causes of eosinophilia were ruled out, and the tuberculin test was negative. Sternal puncture showed many segmented eosinophiles in the marrow. An axillary lymph node showed eosinophilic infiltration. The scattered and changing areas of lung infiltration which were demonstrated by roentgenogram lasted for two weeks and then disappeared.

Within a month the child was again febrile and developed a streptococcus septicemia and a clinical picture resembling aleucemic leucemia. The outcome was fatal. Autopsy added little toward clearing up the etiology of the early lung infiltration.

This case, if it can be accepted as Löffler's syndrome, is one of the few reported in the country. An interesting discussion of whether or not such acceptance can be made is appended to the report.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Further Experiments in the Action of Drugs on the Nasal Mucosa. Proetz, A. W.: Arch. Otolaryng. **30**: 509, 1939.

In studying the action of drugs on the nasal mucosa, Proetz made his observations on the cilia of (1) the living rabbit, (2) extirpated rabbit mucosa, and (3) extirpated human mucosa.

The actions of (1) benzedrine inhalers without oil of lavender and with oil of lavendar and of (2) 1, 2, and 3 per cent solutions of amphetamine in liquid petrolatum were reported as follows:

The benzedrine inhaler without oil of lavender and with oil of lavender showed no deleterious effect on ciliary action.

The direct application of amphetamine stopped all ciliary motion instantly. The application of 1, 2, and 3 per cent solutions in liquid petrolatum caused slowing of ciliary action within a few minutes.

In the same type of experiments it was noted that alcohol in any concentration in distilled water stops ciliary beat in a few seconds, the rapidity depending only on the strength of the solution. When the alcohol was diluted with Locke's solu-

tion, however, it was fairly well tolerated, especially in 5 and 10 per cent dilutions. A 20 per cent solution, however, caused cessation of mitility in 20 to 30 minutes, and the cilia could not be resuscitated.

Agents capable of reducing surface tension, such as decylbenzene sodium sulfonate, monobutyl-diphenyl sodium monosulfonate, and monobutyl-phenyl-phenol sodium monosulfonate, were applied in 0.1 per cent solution. These agents caused disintegration of the epithelial surface and cessation of ciliary action.

The effect of ether, chloroform, and nitrogen monoxide upon the cilia of the trachea as well as of the sinuses of rabbits was also observed. These three anesthetics had no effect per se on ciliary activity when administered in gaseous form. The cold produced by their evaporation may paralyze the cilia while it continues. This was especially notable with ether and chloroform. Actual contact of the fluid, however, was noted to be disastrous to the membrane.

Perennial Hay Fever Diagnosis as Chronic Sinusitis. Black, J. H.: Internat. Clin. **1**: 266, 1938.

Black calls attention to the importance of differentiating between chronic sinusitis and perennial hay fever. Despite roentgenologic evidence of thickened mucosa, more reliance is placed upon the pale mucosa, the watery discharge, and the increase in eosinophiles. With the addition of positive skin reactions, the part played by allergy is of further significance. It is advised that surgical treatment be confined to removal of gross obstructions. Black advises the oral administration of ephedrine or benzedrine in preference to their local application.

Allergic Diseases of the Nose and Sinuses. Opheim, O. F.: Nord. med. tidskr. **16**: 1607, 1938.

Opheim reports his observations on a large number of allergic cases with particular attention to symptoms, operative findings, and histologic sections, and concludes that 25 per cent of all cases may be included under the designation of "rhinosinusitis chronica hyperplastica allergica." Roentgenologic studies and cytologic examinations are emphasized as important in diagnosis. Opheim advises surgical intervention only for major anatomic defects and states that he has had good results from the use of nonspecific desensitization with "novoprotein" (a plant albumin).

The Diagnosis and Treatment of Mucous Nasal Polyps, With a Consideration of the Allergic Factor. Kern, R. A., and Schenck, H. P.: M. Clin. North America **22**: 1633, 1938.

Kern and Schenck express the opinion that polyps are in every instance an evidence of an allergic basis, and they state that avoidance of, or desensitization with, allergens yields clinical results far superior to the old routine of surgical removal alone, with its distressingly frequent recurrence of the polyps. Advice against surgical removal during the pollinating seasons is emphasized. They further advise the removal of polyps only when they are obstructive.

Carcinoma of the Trachea. Olsen, A. M.: Arch. Otolaryng. **30**: 615, 1939.

Although benign and malignant tumors of the trachea are not particularly common, they may simulate bronchial asthma because of the symptoms produced. Olsen reports sixteen cases of carcinoma of the trachea encountered at the Mayo Clinic since 1921. It is pointed out that the symptoms of carcinoma of the trachea are caused chiefly by the action of a group of mechanical factors. The

most common and the most urgent complaint is shortness of breath. The type of dyspnea produced is obstructive in type and should be easily recognized because of the presence of stridor. The dyspnea is frequently paroxysmal and occurs most often at night or when the patient lies down. Cough is present in nearly all instances. At the onset it is usually nonproductive, but eventually it is accompanied by expectoration of mucopurulent sputum. Emphysema and atelectasis may also be present. Olsen further emphasizes that in most instances a diagnosis of asthma is made at some stage of the disease. In the differential diagnosis a great deal of significance should be placed upon the cytology of the bronchial secretions. In the absence of eosinophiles, a diagnostic laryngoscopy and bronchoscopy should be performed at once.

Miscellaneous

Allergic Manifestations With Injection Treatment of Varicose Veins. Shelley, H. J.: J. A. M. A. **112:** 1792, 1939.

The author reviews reactions that occur following the injections for varicose veins with various sclerosing solutions. Salicylates often cause urticaria. Quinine may produce urticaria, dermatitis, and asthma. Sodium morrhuate may cause erythema and urticaria, as well as gastrointestinal disturbances. Deaths have been reported following its use, especially when a considerable interval has elapsed between the first and second series of injections. Reactions are least frequent when non-nitrogenous solutions, such as sodium chloride or sugar, are used.

Determination of Vitamin C Nutrition by Means of a Skin Test. Goldsmith, G. A., Gowe, D. F., and Ogaard, A. T.: Proc. Soc. Exp. Biol. & Med. **41:** 370, 1939.

A skin test for the determination of vitamin C consists in the intradermal injection of 0.01 c.c. of a solution of a dye 2-6 dychlorphenolindophenol. When decolorization occurs in from five to ten minutes the result is considered normal; whereas a decolorization time of over ten minutes implies vitamin C deficiency. The test was done on 45 persons on whom 100 observations were made. There was no correlation between the vitamin C content of the blood and the skin test which indicated vitamin C in the tissues.

Periarteritis Nodosa. Harris, A. W., Lynch, G. W., and O'Hare, J. P.: Arch. Int. Med. **63:** 1163, 1939.

Six cases of periarteritis nodosa were described, and many of the previously reported cases were reviewed in view of the contention that the lesions are due to irreversible allergic processes in the walls of the vessels. In this series only one gave a history of allergic manifestations; and in a history of 101 cases that were reviewed, the history of allergy was obtained in but 19.

Ergotamine Tartrate in the Treatment of Serum Sickness. Chalier, J., and Rion, J.: Lyons méd. **161:** 541, 1938.

Ergotamine tartrate, given 1 mg. by mouth three times a day, was effective in relieving the itching of serum sickness, although it had no effect on any of the other symptoms.

Histaminase in the Treatment of Serum Sickness. Foshay, L., and Hagebush, O. E.: J. A. M. A. **112**: 2398, 1939.

Eight patients with serum sickness were given enteric-coated tablets of histaminase during the first three days of symptoms. Six patients had some relief. Another series of 13 patients were treated with intramuscular injections of histaminase, which at times were combined with oral administration, and all patients received marked relief from symptoms. Moreover, patients treated both orally and parenterally with histaminase before the administration of serum did not develop serum sickness. No untoward reactions to the drug were encountered.

Susceptibility to Serum Sickness. Beer, A.: Ztschr. f. Kinderh. **60**: 418, 1938.

The author analyzed cases of serum sickness in patients who had received diphtheria antitoxin over a period of twenty years (1916-1935). He noted an increase in percentage incidence during the spring months. Age had little to do with its appearance, whereas there was a definite relationship between the age of the patient and the presence of joint manifestations. There was a direct ratio in that the older the child, the greater the tendency to arthralgia. Moreover, joint symptoms appeared earlier in the disease in older children.

Nonspecific ''Desensitization'' Through Histamine. Farmer, L.: J. Immunol. **36**: 37, 1939.

Guinea pigs sensitized to serum were given increasing amounts of histamine by intra-abdominal injections at intervals of one to three days for a period of twelve to eighteen days. The first dose was given thirteen to fifteen days after the sensitizing injection of serum, i.e., at a time at which animals usually are highly sensitized. Uterine strips were examined twenty-six to thirty-six days after sensitization. They were found to be less sensitive to the specific antigen than were the sensitized uterine strips of control animals. The uterine strips of normal guinea pigs that had received injections of histamine were less sensitive to histamine than were the uterine strips of untreated controls. These experiments suggest that histamine is the substance responsible for the anaphylactic contraction of plain muscle and that it is possible to ''desensitize'' sensitized guinea pigs nonspecifically by injections of histamine.

Erratum

In Tables III, IV, V, and VI, pages 540 to 543, of the article, ''Immunologic Relationship of Giant, Western, Common Ragweed and Marsh Elder (Iva ciliata),'' by Homer E. Prince and P. G. Secrest, Jr., J. ALLERGY **10**: 537, 1939, the word ''unit'' following the fractional serum dilution at the bottom of each table should be omitted. The serum dilutions should read 1/10, 1/30, 1/100, 1/300, and 1/1,000.

Book Reviews

Practice of Allergy. WARREN T. VAUGHAN, M.D. St. Louis, 1939, The C. V. Mosby Co., pp. 1082, illustrated.

Of that part of allergy designated as atopy, this book is monumental in its scope. Until a great deal more is learned about the subject it will probably stand as a landmark to indicate the accumulated knowledge of this topic brought up to date. The usefulness of such a book depends so much upon a proper sequential presentation of its subject matter so that one may turn readily to the pages which contain the information that is sought. Dr. Vaughan has achieved this in the construction of his book.

The subject matter consists of material which is recorded under conventional titles, but the wealth of detail makes for completeness. For instance, under food allergens are not only botanic classifications but great detail concerning species and families and their relation to each other. The same holds true of edible animal foods, with a wealth of information concerning food allergens. Plants that cause hay fever are handled in a similar way.

In addition to the discussion of atopy, a considerable space is devoted to contact dermatitis, and the essential factors of physical allergy, serum allergy, and drug allergy are stated.

Emphasis on the fundamental aspects of allergy is testified to by the fact that, of 1,034 pages of such matter, less than 100 are devoted to allergic diseases per se, although a clinical point of view is maintained throughout the book.

Although books on allergy doubtlessly will continue to appear, original contributions will of necessity be points of view rather than the assembling of material which has been done in this book. There is an extensive and complete bibliography. As a reference work this book has great value.

Primer of Allergy. WARREN T. VAUGHAN, M.D. St. Louis, 1939, The C. V. Mosby Co., pp. 140, illustrated.

This little book is written solely for the laity and thus differs from several others which have attempted to combine that audience with the general practitioners. Moreover, it is addressed to those of simple intelligence and hence appears as a primer. It is written in a facetious vein with humorous illustrations. The serious mother of an allergic child may not see the fun of it, but she will read the message, for it is there.

Allergists are well served by many textbooks, but there is a paucity of proper information for the patient, and that is what this primer contains. It will doubtless be in much demand.